THE ASSOCIATION BETWEEN OBSTRUCTIVE JAUNDICE AND RENAL FAILURE.

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CONTENTS

INTRODUCTION

Kidney dysfunction in association with liver disease has been recognised for 100 years. (Austin Flint, 1863)

The alterations in renal function associated with virus hepatitis and cirrhosis of the liver have been fairly extensively studied, and have been the subject of excellent reviews. (Hecker and Sherlock, 1956, Papper, 1958, Papper et al, 1959, Eisner and Levitt, 1961, and Papper, 1963) Similarly, yellow fever, leptospirosis and many poisons may produce both hepatic and renal damage and must be considered, where disease of both organs is found. (Spellberg, 1954, Popper and Schaffner, 1957 and Cohen et al, 1957) Renal failure is well recognised in patients with obstructive jaundice, but this has been the subject of much less study. The present investigation is confined to a study of the effect of obstructive jaundice on renal function and to the relationship between bile duct obstruction and renal failure.

A review of the literature shows that renal failure developing in patients with obstructive jaundice, most commonly follows surgery to the biliary tract. In the latter part of the nineteenth century, reports in the French and German literature drew attention to the association. (Frerichs, 1858, Merklen, 1881 and Quincke, 1899) In the nineteen twenties and thirties a succession of papers discussed the subject under such titles as "Liver Death," "Hepato-Renal Syndrome" and "Uro-hepatic syndrome." (Walters and Parham, 1922, Heyd, 1924, Cave, 1926, Stanton, 1930, Schutz et al, 1932) More recently Williams et al (1960) reported an incidence of fatal uraemia in 6% of 350 patients, who had had surgical treatment of obstructive jaundice and study of the records of patients admitted for treatment of acute renal failure to haemodialysis units, showed that 34% of one series of 132 patients had biliary tract disease, 21 with jaundice, (Andreassen et al, 1961) and 31% of another series (Balsløv and Jørgensen, 1963) followed surgery to the biliary system.

Therefore, even though the papers written before the nineteen forties often fail to distinguish between the various causes of jaundice or to consider the role of haemorrhage, sepsis and other complications in the aetiology of the renal failure, there is considerable evidence to suggest a special association between the two conditions. (Malm, 1952, Williams et al 1960, Andreassen et al, 1961 and Balsløv and Jørgensen, 1963)

There are many histological studies of the kidney in patients with obstructive jaundice. (Wilbur, 1934, Lieber, 1935, Ayer, 1940, Lucké, 1944 and Allen, 1962) The appearances in experimental animals subjected to bile duct ligation are essentially similar. (Stewart et al, 1935, Thompson et al, 1940 and Uys, 1957) Glomerular changes are slight and the main changes are seen in the proximal tubules and include bile pigmentation and varying degrees of hydropic vacuolation. Frank tubular necrosis is uncommon. Apart from the bile pigmentation, these changes are in no way specific.

In patients with obstructive jaundice, dying with acute renal failure, the appearances found are those already described with, in addition, the changes typical of acute tubular necrosis. (Malm, 1952 and Lassen and Thomsen, 1958)

In contrast to the numerous studies of renal histology, there are relatively few studies of renal function in jaundice and there is no unanimity as to the frequency or degree of kidney impairment in this condition. In many reports, normality of renal function has been claimed on the basis of blood urea or non-protein nitrogen levels only. (Bartlett, 1933, Wilbur, 1934, Meyers et al, 1935,and Ayer, 1940) There are few reports of actual measurements of glomerular filtration rate and the results of these studies vary widely, although all show some degree of reduction in filtration rates. (Elsom, 1937, Popper and Mandel, 1937, Meyer et al, 1941, Schmidt and Chesky, 1948, Cavazutti et al, 1952, Paris, 1953, Giraud, 1955 and Nociti, 1958)

Despite the fact that the main pathological changes seen are tubular and not glomerular, even fewer studies of tubular function have been undertaken. Defects in urine concentration (Thompson et al., 1940), renal excretion of water (Paris, 1953 and Giraud, 1955) and sodium reabsorption (Giraud, 1955) have been described.

Only one paper can be found with details of renal blood flow in obstructive jaundice (Nociti, 1958), and little is known of the effect of haemorrhage or hypovolaemia on the renal circulation in this condition. Williams et al. (1960) suggest that haemorrhage results in more marked impairment of renal blood flow in jaundiced, than in non-jaundiced patients.

In the present study, the effect of jaundice on renal glomerular and tubular function has been investigated in detail. The evidence for a special association between obstructive jaundice and acute renal failure has been reviewed and possible reasons for this association have been considered.

PRESENT INVESTIGATION

The object of this study was to establish whether or not uncomplicated obstructive jaundice affects renal function, and to study certain factors which might operate in the presence of jaundice to predispose to acute renal failure.

MATERIAL.

Studies of renal function were performed on patient, admitted to a general hospital with obstructive jaundice, and in addition investigations were carried out on dogs, in whom jaundice was induced by bile duct ligation. The material, methods and results for the two groups will be considered separately.

Human Studies: Material

All patients admitted to Saint Bartholomew's Hospital, London, between September, 1960 and June, 1963, with obstructive jaundice were considered for this study. In order to exclude cases with pre-existing hepatic disease, no patient was included, who gave a history, suggestive of virus hepatitis, cirrhosis of the liver, or drug or chemically induced liver disease. In addition, only patients with normal serum protein levels and normal thymol turbidity and zinc sulphate flocculation tests were included.

Patients with active urinary infection were also excluded from the study. This was judged to be present if bacterial counts of more than 100,000 organisms per ml. were found in an early morning specimen of urine. At least two specimens were obtained from each patient. Patients aged 70, or over, were not included in the investigation, because it was felt that the renal sequelae of jaundice and those of old age might be difficult to distinguish. At the commencement of the study, it was proposed that severely dehydrated or cachectic patients be excluded, but in practice this was not necessary.

All patients studied, were required to have had jaundice for at least two weeks prior to study - a time considered likely to be sufficient for any renal manifestations of jaundice to become detectable. They all had serum bilirubin levels of 5 mg./100 ml. or more, elevated serum alkaline phosphatase levels, bilirubinuria and bile salts present in the urine. A careful note was made of the clinical state of all patients with regard to fever, dehydration or associated systemic disease, likely to affect renal function; particular note was taken of the presence of hypertension or previous renal disease.

During the period of the study, 32 patients with obstructive jaundice were admitted to Saint Bartholomew's Hospital, who fulfilled the above criteria. It was not possible to study 11 of these patients, because facilities for study prior to operation were not granted. However, careful appraisal of the case records of these 11 patients gives no reason to believe that they differed in any significant way from the 21 patients, who were studied and failure to include them should not bias the findings in the remainder. In addition, 4 patients were seen and studied at the Whittington Hospital, London. Their selection was entirely random and involved the same criteria as the Saint Bartholomew's patients.

A further 3 patients were admitted to the hospital during the study period, who had obstructive jaundice and already established renal failure.

At the start of the study, it was hoped that it would be possible to perform renal function studies on all patients before and after the relief of jaundice and in this way define the extent to which any abnormality was related to the jaundiced state. It soon became apparent, however, that there was a high incidence of jaundice due to carcinoma and a low incidence of simple gall stone obstruction or bile duct stricture; while palliative surgery relieved the jaundice in the majority of the cancer patients, their clinical condition deteriorated rapidly, due to the malignant disease and post-operative studies were precluded by their poor condition.

For this reason and also to permit studies on the effect of haemorrhage on renal function in the presence of obstructive jaundice, it was decided to embark on a series of animal experiments in which the renal function of dogs was studied before and after bile duct ligation and again after subsequent cholecyst-jejunostomy.

Case abstracts concerning all the patients studied are included in the Appendix, together with clinical details of other patients seen who developed renal failure while jaundiced. The salient facts concerning their illnesses are given in Tables 1, 2 and 3. (Pages 36, 37, 38)

Methods of study

All patients were seen as soon as possible after their admission to hospital, when a detailed history was obtained and a full clinical examination performed. The purpose and nature of the study was explained to all suitable patients and if agreeable they were subjected to the following standard programme of investigation.

1) Measurement of glomerular filtration rate (G.F.R.) and effective renal plasma flow (E.R.P.F.) using Inulin and Para-amino-hippurate (P.A.H.) clearance rates respectively. Endogenous creatinine clearance studies were also performed on most patients and in a few were the only measure of glomerular filtration rate as the patients were unwilling to undergo the more elaborate Inulin and P.A.H. clearances.

2) Examination for proteinuria. Six specimens of urine, obtained at different times of day and including at least two

early morning collections were tested for protein. In addition, each patient had at least one 24-hour urine collection examined quantitatively for protein and where excretion of this exceeded 100 mg. per day, the urine was concentrated and protein electrophoresis performed.

3) The same specimens of urine were examined for the presence of sugar and if this was present, standard glucose tolerance tests were carried out.

4) Twenty-four hour urine collections were examined qualitatively for evidence of abnormal amino-aciduria in the first 13 patients, using two-dimensional paper chromatography.

5) Urine concentrating ability was tested by measurements of urine osmolality following the subcutaneous injection of vasopressin tannate in oil.

6) The capacity of the kidney to acidify the urine was measured using the short test of urine acidification introduced by Wrong and Davies (1959).

7) The renal conservation of sodium was examined following the oral administration of 9α-fluoro-hydrocortisone in 9 patients, and the results compared with those obtained in 7 non-jaundiced controls.

8) Blood volume estimations were carried out on 14 patients using $Cr._{51}$ labelled red cells.

Details of the methods employed in each of these investigations is given in Appendix 2.

Results

Twenty-five patients were studied, of whom 16 were male and 9 female. Their ages, the cause of their obstructive jaundice and the most important biochemical findings are summarised in Table 1.

In age, the male patients ranged from 40-66 years (Mean, 56.6 years) and the female patients from 39-65 years (Mean, 56.1 years). Their serum bilirubin levels varied between 5.0 and 25.0 mg./100ml., with a mean value of 11.2 mg./100 ml. for men and 11.8 mg./100ml. for women, with an even distribution about these means. Blood urea levels varied between 24 and 48 mg./100 ml. (Normal values for the same laboratory are 15-45 mg./100 ml.) The values all tended to be in the high normal range and one was above normal.

G.F.R. and P.A.H. Clearance

Inulin and P.A.H. clearances were carried out on 20 of the 25 patients. One patient declined to have the test performed and four patients were investigated at another hospital, where it was not possible to undertake this investigation. In all 5 of these patients, endogenous creatinine clearances were performed. As simultaneous Inulin and creatinine clearances were performed on 16 patients, it is possible to calculate the ratio of Inulin to creatinine clearance obtained in our laboratory, and hence to calculate endogenous creatinine clearance for all the patients seen. The results obtained are shown in Table 4. (Page 39)

In male patients, Inulin clearances (C_{IN}) varied from 70 to 122 ml./min., with a mean of 101.8 ml./min. (S.E.*±4.9).

In females, values of 75-121 ml./min. were obtained, with a mean of 98.9 ml./min. (S.E.± 4.9).

These values may be compared (Table 5, Page 40) with the normal values obtained by Smith (1951) using similar methods. Normal values obtained in our laboratory agree with the more extensive data of Smith. In neither male nor female patients is the glomerular filtration rate grossly reduced. Values below 90 ml./min. being obtained in only 3 males and 1 female. The general impression given is of slight to moderate reductions in Inulin clearance. Statistical analysis of the results in comparison with those of Smith shows (Table 5) that the reduction in Inulin clearance is significant (P less than 1%) in the case of male patients, but does not quite reach the 5% level of significance in female patients.

Clearances of P.A.H. also showed only slight to moderate reductions, although values less than half normal were obtained in two male patients.

The mean value for male patients was 454.7 ml./min. (S.E.±34.4) compared with a normal of 654.0 ml./min. (S.E.±29.0).

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*S.E. = Standard error of the mean.

For female patients the mean was 478.9 ml./min. (S.E.±31.7); normal 592.0 ml./min. (S.E.±46.1).

The reduction was again significant in the case of the male patients, but not for females.

Endogenous creatinine clearance data, which included studies on the 5 patients not studied by means of Inulin clearances, showed the same trend (Table 6, Page 41). The mean value obtained for the male patients was 102.2 ml./min. (S.E.±3.6) and for female patients 103.2 ml./min. (S.E.±5.5).

Normal values obtained in this laboratory are 116.0 ml/min. (S.E.±3.8), for males, and 107.0 ml./min (S.E.±4.2) for females. Again the reduction in the clearance rates proved to be significant for males, but not for females.

The mean filtration fraction calculated for both men and women was slightly higher than the normally accepted value (Smith, 1951). In the case of the males, the difference was statistically significant.

Relief of jaundice and restoration to normal health was achieved in only 10 of these 25 patients. Of the remainder, 3 died, 2 of acute renal failure following operation and one from massive pulmonary embolism. The remaining 12, although their jaundice was relieved to a variable degree by palliative surgery, deteriorated clinically, due to underlying cancer. There were, therefore, only 10 patients in whom further studies could be performed after full recovery from obstructive jaundice.

It was possible to undertake Inulin and P.A.H. clearances in 6 of these 10 patients and endogenous creatinine clearances in a further 3. These studies were performed at least 4 weeks after the disappearance of jaundice (Table 4). In no instance, was there any significant change in Inulin, P.A.H. or creatinine clearances. It should be noted, however, that in 5 of the 6 patients studied by Inulin and P.A.H. clearances, the values obtained while jaundice was present fell within the normal range. This was also true in 2 of 3 cases in whom only creatinine clearances were performed.

Post-mortem examinations were obtained on the two patients (one male and one female) who had been found to have the most marked reductions in glomerular filtration rate and P.A.H. clearance. In both cases, marked nephrosclerosis was found.

Creatinine clearances were performed on 15 of the jaundiced patients before and 7-9 days after operation. For comparison, similar studies were carried out on 17 randomly selected non-jaundiced patients undergoing cholecystectomy and on 5 patients having partial gastrectomies performed. (Tables 7 and 8, Pages 42, 43) These studies were carried out when the patients were considered to be fully and equally hydrated. Both groups showed small percentage decreases in creatinine clearance (jaundiced patients, -6.7%±3.8; non-jaundiced -7.6%±2.4). There is no significance between the two groups in respect of these reductions.

Many factors affect the interpretation of these results and these are considered in detail in the discussion.

Two patients developed post-operative renal failure. In one of these, pre-operative clearances of Inulin and P.A.H. were within normal limits. In the other, only an endogenous creatinine clearance was obtained before operation, but this too was normal. There is, therefore, no evidence in these patients that the post-operative renal failure could be related to pre-operative glomerular insufficiency.

<u>Proteinuria.</u>

Five of the 25 patients were found to have proteinuria (Table 9, page 44). This varied in amount from 200 to 800 mg./24 hours and may, therefore, be considered slight. In all instances one dimensional paper electrophoresis showed a predominance of albumen. No bands of abnormal protein were demonstrated, using this technique. The incidence of proteinuria could not be correlated with the degree or duration of jaundice. One of the patients in whom it was found, was subsequently shown at necropsy to have marked nephrosclerosis (Case 5) and another gave a previous history of renal calculi and urinary infection, (Case 10) both conditions known to be associated with proteinuria. Jaundice was relieved in two of the five patients and in one (Case 19) the proteinuria disappeared following this. The other patient is the case already referred to as having a previous history of calculi, in whom the proteinuria persisted.

We concluded from these results that there was a significantly high incidence of proteinuria in this small series, but that the proteinuria was not large in amount and on electrophoresis, was of the type usually associated with glomerular damage. In the one patient, in whom there was no evidence of associated renal disease and who was subsequently returned to normal health, the proteinuria disappeared.

Tests of Tubular Function

Glycosuria

Glycosuria was found in 3 of the 25 patients (Table 9). In each instance, this was associated with a diabetic type of glucose tolerance curve and occurred in association with carcinoma of the pancreas. There was no evidence to suggest acquired renal glycosuria secondary to obstructive jaundice.

Amino-aciduria

The urine amino-acid pattern was examined by two-dimensional paper chromatography in 13 patients (Table 9). The pattern was normal in every case. It may be concluded that in the patients studied, obstructive jaundice was not associated with amino-aciduria of the mixed type described in association with other types of acquired tubular disease (Bickel, 1962).

Urine Concentrating Ability

None of the patients seen gave a history of excessive thirst or polyuria. None had evidence of dehydration, which could not be readily explained on the basis of extra-renal losses of fluid. All were normally hydrated at the time of study. The capacity of the kidneys to produce concentrated urine in response to sub-cutaneous injection of vasopressin tannate in oil, was studied in all the patients (Table 9). The maximum osmolality varied between 780 and 1024 m.osmol./kg. with a mean of 935 m.osmol./kg. (S.E.$\pm$16). These values are within the normal range obtained in this laboratory using the same method, in patients of comparable age. These values do not necessarily representmaximum renal concentrating ability as higher values can be obtained with the more stringent fluid deprivation test (de Wardener, 1956). They do, however, demonstrate that no clinically significant defect in fluid conservation by the kidney, results from the presence of obstructive jaundice.

Acidification of the Urine

Defective tubular function may be manifest by an inability to excrete an acid urine in response to acid loads. Severe defects of this type are characterised biochemically by hyper-chloraemic acidosis. None of the patients studied had any evidence of this. The ability of the kidneys to secrete acid urine was further tested in 21 patients, using the short test of urinary acidification devised by Wrong and Davies (1959). The minimum urine pH achieved by these patients is given in Table 9. More complete details, including urine flow rates, minimum pH values and rates of excretion of ammonium, titratable acid and total acid excretion are given in Table 10, page 45 for 16 of the 21 cases.

The same table gives the range of values obtained, using the same test, in 12 normal persons, aged 26 to 45 years. In patients with jaundice, the range of minimum urine pH values was 4.78-5.77 with a mean of 5.26±0.05. Normal values varied between 4.60 and 4.92 (Mean 4.74±0.04). This difference is statistically significant (P less than 1%). Five of the 16 patients were given Ammonium Chloride 8G. daily for 3 days and the test was repeated. No further reduction in the minimum pH was obtained. Four patients were studied after the relief of jaundice (Table 11, page 46) and all showed lower urine pH values in response to the same dose of Ammonium Chloride. We conclude, therefore, that obstructive jaundice is associated with a slight abnormality in the kidney's ability to secrete acid urine. This abnormality is reversible. The functional defect is slight and does not amount to fully developed renal tubular acidosis as defined by an inability to secrete urine more acid than pH 5.0 in response to an Ammonium Chloride load (Wrong and Davies, 1959. Milne, 1963).

The rate of excretion of titratable acid was within normal limits, but in the low normal range and was inversely related to the minimum urine pH. Ammonium excretion was high normal or slightly above normal but bore the normal relationship to urine pH. This test was not designed to measure the kidney's capacity to secrete titrable acid or ammonium. The values obtained for the excretion of these substances are compared with values obtained in healthy subjects, using the same test and are normal in this context only.

Sodium Conservation

The ability of the kidneys to conserve sodium in the presence of jaundice, was assessed in 9 patients. For this purpose, a short test was devised in which the 24 hour urinary excretion of sodium was measured during the administration of 4 mg. of 9-α-fluorohydrocortisone daily, for 3 days. The sodium excretion rates observed in jaundiced patients were compared with the results obtained in 7 non-jaundiced ward patients aged 29-62 years. (Table 12, page 47) The lowest value for the 24 hour sodium excretion is given. This was usually obtained on the third day, although in most instances similar values were obtained on the second and third days. The time available for the study did not allow continuation of the test until minimum sodium excretion was demonstrated. The lowest 24 hour sodium excretion values obtained in jaundiced patients ranged from 11-21 m.eq. with a mean of 16. In non-jaundiced patients, values of 10-17 m.eq./24 hours (mean 14) were observed. The presence of cancer did not appear to affect the results. There is no statistical difference between these results. It is concluded that jaundiced patients show a normal capacity to conserve sodium in response to 9-α- fluorohydrocortisone.

Blood Volume Measurements

Red cell volume was measured in 14 patients using Cr_{51} labelled red cells and from this and the venous haematocrit, blood volume and plasma volume were estimated. The expected blood volume and plasma volume for each patient was also calculated, using a surface area formula (Appendix 2). These results are given in Table 13 (page 48). The difference between measured and expected values is expressed as a percentage of the former. The measured blood volume exceeded the predicted blood volume in 10 of 14 patients, the mean increase for the group as a whole being +4.3%$\pm$1.66 (Table 14, page 49). In the case of plasma volume, the whole group showed a mean increase of 8.1%$\pm$2.5, two patients only showing values below that predicted. In both instances, these increases are statistically significant (Table 14). The difference in percentage increases in plasma volume and whole blood volumes reflects reductions in venous haematocrits in both males and females (Table 13) and indicates reduced red cell mass (anaemia) with compensatory increases in plasma volume.

The results calculated in this way indicate that blood volume is maintained at normal levels in presence of obstructive jaundice. The validity of such calculations is dealt with in some detail in the discussion of these results.

Animal Studies: Material

This study was begun in June, 1962 and completed in August, 1963 and was carried out in the Department of Physiology, the Royal Veterinary College, London.

Dogs trained for renal function studies were not available and because of the limited number of kennels provided (four) and the time and expense involved in training dogs, it was decided to perform all the studies on lightly anaesthetised animals. It was fully appreciated that there are objections to the use of anaesthetised dogs for renal function studies, (Smith, 1951) but as each dog was studied under identical conditions of fluid loading and anaesthesia and acted as its own control, it was considered that valid information could be obtained. Twenty-one mongrel bitches were used and every attempt possible made to obtain young animals weighing between 25 and 35 lbs. Urine cultures, blood urea and serum bilirubin estimations were performed on all animals and no dog included with pre-existing urinary infection, azotaemia or jaundice.

Methods

All dogs were maintained on a standard kennel diet and were weighed at weekly intervals. During the first 2 or 3 weeks, basal studies on renal function and blood volume were performed. These and all subsequent studies were carried out on fasting animals under light pentobarbitone anaesthesia. The amount of anaesthetic used was calculated on a body weight basis and every effort made to obtain a standard depth of anaesthesia. Less anaesthetic was required in jaundiced animals. All dogs were intubated with endo-tracheal tubes and catheterised with strict aseptic precautions, a urine sample being sent for culture on each occasion.

Following completion of basal studies, obstructive jaundice was produced by bile auct ligation. All dogs were operated on by the same surgeon (M.A.B.). The common bile duct was dissected free, doubly ligated and divided, a segment of duct 0.5-1.0 cm. long being removed. A careful search for accessory ducts was made in all instances, but none found.

After surgery all dogs were established on Tetracycline 250 mg. orally on alternate days. This drug was administered because of a reportedly high incidence of cholangitis and liver abscess, following bile duct ligation in dogs. (Williams et al., 1960) Penicillin was avoided because of possible interference with P.A.H. excretion. All but the first 3 dogs were given intra-muscular Vitamin K (Synkavit) 10 mg. twice weekly. In the first 6 dogs, serum bilirubin levels were measured weekly.

In the remaining animals serum bilirubin was estimated 4, 5 and 6 weeks after bile duct ligation.

Six weeks after jaundice had been induced, the same studies, which had been performed before jaundice were repeated. In 8 dogs, surgical relief of jaundice by cholecyst-enterostomy was subsequently attempted, but was technically difficult and only proved successful in 4 on whom studies were performed four to six weeks after the relief of jaundice.

Studies Performed

Glomerular filtration rate (Inulin clearance) and effective renal plasma flow (P.A.H. clearance) were measured on all dogs under the same conditions of anaesthesia and fluid loading, before and after the production of jaundice. To establish the reproducability of the results obtained, clearance studies were performed on two separate occasions on 10 dogs before and on 9 dogs during jaundice. In 4 dogs clearances were also performed after the relief of jaundice.

The renal extraction of P.A.H. was determined in 5 normal and 5 jaundiced dogs.

Blood volume estimations were carried out on all dogs, before and during jaundice using Evans Blue dye.

The effect of controlled haemorrhage on the systemic blood pressure, glomerular filtration rate and effective renal plasma flow, before and during jaundice, was investigated. In 10 dogs, the effect of moderate haemorrhage was studied. Inulin and P.A.H. clearances were first carried out under basal conditions. In all instances, 2 and usually 3 urine collection periods were employed. Mean systolic blood pressure was recorded via a catheter inserted into the femoral artery. Blood volume estimations were performed during this initial period. Haemorrhage was then effected via the femoral artery cannula, the blood being collected in a sterile, heparinised container. Initially sufficient blood was removed to reduce the estimated blood volume by 15%, (the precise percentage of the blood volume removed was calculated in retrospect when the actual blood volume measurement had been carried out). Twenty to thirty minutes were allowed to elapse and further clearances were performed. More blood was then withdrawn, calculated to reduce the blood volume by a total of 30% and again clearances carried out after an interval of 20-30 minutes. The blood pressure was recorded throughout. On completion of the final clearance period the blood withdrawn was returned by slow intravenous infusion. These studies were repeated on the same animal under the same conditions six weeks after the production of obstructive jaundice.

In a further ten dogs, the effect of severe haemorrhage was studied. Again basal Inulin and P.A.H. clearances were performed, blood volume measured and systemic blood pressure recorded. Subsequently sufficient blood was withdrawn to produce a lowering of the systemic blood pressure to between 60 and 70 mm. Hg. The amount of blood removed to effect this was recorded. Hypotension of this order was maintained for ninety minutes. This occasionally required further withdrawal of small amounts of blood or less commonly re-infusion of blood. During this period intravenous infusions of Inulin and P.A.H. were reduced to the minimum required to maintain the infusion cannula patent. At the end of ninety minutes, the blood was returned to the animal and the rate of Inulin and P.A.H. infusion increased. Thirty minutes after the blood had been replaced, further clearance studies were performed and repeated at 60 and 90 minutes. To assess any delayed effect of the procedure on renal function, clearances of Inulin and P.A.H. were measured after an interval of 7-10 days. Identical studies were carried out on the same animals after 6 weeks of obstructive jaundice.

Details of the clearance techniques, methods of blood pressure recording and blood volume estimations afe given in Appendix 2.

Results

Studies were performed on 21 dogs. Four of these dogs died before the studies were completed, however, none of the 4 died of renal failure, all having normal blood urea levels at the time of death. One animal died from bile peritonitis and 2 died within 12 hours of operation, without fully recovering from the anaesthetic. The fourth dog died suddenly 3 weeks after operation and no obvious cause was discovered.

Following bile duct ligation the remaining 17 dogs recovered satisfactorily and were eating and drinking normally within 24 hours. In the next 4 to 6 weeks, during the development of increasing jaundice the dogs in general became less active and rather drowsy. Food and fluid intake was well maintained either spontaneously or by hand feeding.

Jaundice developed fairly rapidly and was well established within 2-3 weeks. Thereafter serum bilirubin levels either remained constant or progressively increased. No explanation can be given for this difference in response. Serum bilirubin values obtained in normal dogs were all between 0.1 and 0.4 mg./100 ml. The value obtained at the time of further study 4-6 weeks after bile duct ligation are given in Table 5 and varied between 4.5 and 18.6 mg./100 ml. (Mean 9.9 mg./100ml. ± 1.08).

All dogs lost weight, which varied between 4 and 24% of the animal's initial weight (Mean 15.9%±1.62) - Tables 15 and 16, pages 50, 51.

The mean systolic blood pressure was recorded in all dogs studied during light general anaesthesia before and after bile duct ligation (Table 15). Although every effort was made to control the conditions under which the estimations were carried out and the value given is the mean of many recordings taken over 30-60 minutes, considerable lability of the pressure was noted during the studies. In the majority of dogs (12) lower values were obtained in the presence of jaundice and when expressed as a percentage of the blood pressure recorded before jaundice, the mean difference was -8.3% ± 4.09. This, however, is not statistically significant. (P greater than 5%).

Glomerular Filtration Rate and Effective Renal Plasma Flow

The results of the renal clearance of Inulin and P.A.H. before and 4-6 weeks after the production of jaundice are available for 17 dogs. There was a wide scatter obtained for Inulin and P.A.H. clearance in dogs without jaundice. These differences arise from variations in weight, body size and age. To ensure that the animals had relatively normal kidney function, clearance values obtained at the commencement of the study were calculated on the basis of body weight and corresponded to the normal values given by Smith (1956). Subsequently as each animal served as its own control, differences before and after jaundice were expressed as the percentage change from the initial value. The errors inherent in correcting clearance data for body size are thus avoided.

In order to be sure that the clearance values obtained were reproducible under the conditions of our experiments, Inulin and P.A.H. clearances were measured on two separate days in 10 dogs without jaundice and also in 9 dogs with jaundice. The results are given in Table 17, page 52.

There was remarkably good correlation between the values obtained on the two separate occasions in both jaundiced and non-jaundiced dogs.

The values for Inulin and P.A.H. clearance, renal blood flow and filtration fraction in each dog, before and during jaundice are given in Table 15.

The glomerular filtration rate decreased in 13 dogs in the presence of jaundice and increased in 4. The mean change for the group as a whole was -19.7% ± 6.07 (Table 18, page 53). This reduction in Inulin clearance is significant (P less than 0.1%). The percentage change in Inulin clearance was compared with increases in serum bilirubin, systemic blood pressure, blood volume and plasma volume and the correlation co-efficients are given in Table 19, page 54. The only correlation demonstrated was between serum bilirubin level and Inulin clearance. (P less than 5 but greater than 1%) Inulin clearance was measured in 4 dogs before, during and after jaundice. (Table 20, page 55) Glomerular filtration rate fell in all 4 dogs during jaundice, rising again to normal values after its relief. This group is small, but the constancy of response to jaundice is impressive.

P.A.H. Clearance showed a mean reduction of -12.7% ± 5.53 in the presence of jaundice (Table 18). This reduction is less than that demonstrated with Inulin clearance, but is still significant. (P less than 1%) In the 4 dogs in whom this was studied after relief of jaundice, a return to normal values was again demonstrated (Table 20). The reduction in P.A.H. clearance showed no significant correlation with changes in serum bilirubin, weight, systemic blood pressure, plasma or blood volume (Table 19).

The renal extraction of P.A.H. was determined in 5 normal and 5 jaundiced dogs. The extraction ratio for P.A.H. in normal dogs was 85.4% $\pm$1.2 and in the jaundiced dogs 86.0% $\pm$0.8. No difference has, therefore, been demonstrated in the extraction of P.A.H. by the kidney in jaundiced as compared to normal animals. Both values are comparable to the normal values quoted by Smith (1951). With this knowledge, it is possible to state that the reductions demonstrated in P.A.H. clearance represent reduction in effective renal plasma flow.

Renal blood flow has been calculated from P.A.H. clearance and the venous haematocrit. No correction was made for the extraction rate of P.A.H. In the presence of jaundice, renal blood flow fell by a mean value of 14.2% $\pm$5.92. The difference between the reductions in renal blood flow and P.A.H. clearance reflect the fall in venous haematocrit values found during jaundice.

The mean filtration fraction value was reduced by 6.2% $\pm$5.1 in the jaundiced animals (Table 18). This reduction is not significant. In summary, these results show that the production of obstructive jaundice in dogs is accompanied by small but significant reductions in the mean values obtained for Inulin and P.A.H. clearances, and renal blood flow. The decrease in Inulin clearance slightly exceeds the reduction in P.A.H. Clearance, but this did not lead to a significant change in the mean filtration fraction. These changes could not be related to alterations in weight, systemic blood pressure or blood or plasma volume, but a probably significant correlation was found between the fall in glomerular filtration rate and the rise in serum bilirubin.

The effect of haemorrhage on renal function in dogs.

A. Mild and moderate haemorrhage.

Studies on the effect of moderate haemorrhage on renal function in the same dog, before and during jaundice were undertaken in 10 dogs. Complete data is available for 8 dogs only, as one died during the second period of study and clearance values obtained for the remaining animal, when jaundiced, were so variable as to be worthless. As explained under methods, Inulin and P.A.H. clearance were measured in the resting state and again after removal of an estimated 15% (mild haemorrhage) and 30% of the blood volume (moderate haemorrhage). The same procedure was carried out on each dog before and during jaundice.

In order to compare the effect of haemorrhage on glomerular filtration rate and P.A.H. clearance in jaundiced compared with non-jaundiced dogs, we have had to employ a method which at first sight appears rather complicated. Thus, the percentage change in these values following bleeding in jaundiced dogs is subtracted from the same value obtained in the same dog before jaundice. No difference in response will, therefore, be evidence by a zero value. A smaller fall in clearances in jaundiced dogs will give a negative value, while a greater fall will give a positive value. Only in this way can we make allowances for different initial values for Inulin and P.A.H. clearances. The actual values obtained and the percentage changes are given in Table 21, page 56. This table also shows the change in mean systolic blood pressure following haemorrhage in these dogs. The extent of the haemorrhage expressed as blood removed as a percentage of the blood volume measured at the same time is shown in Table 22, page 58.

Jaundice affected the response to haemorrhage as measured by Inulin and P.A.H. clearance, in a widely different manner in separate animals. Statistical analysis shows no significant difference in the mean response to haemorrhage in jaundiced compared with non-jaundiced dogs (Table 23, page 59). The evidence collected indicates that the effect of mild or moderate haemorrhage on glomerular filtration rate and P.A.H. clearance is not consistently altered in the presence of jaundice.

Haemorrhage of between 10 and 23% of the total blood volume produced very small changes in the mean systolic blood pressure

(Table 20). In the presence of jaundice haemorrhages of the same order produced slightly greater changes in blood pressure, but the difference did not reach the 5% level of significance (Table 24, page 60). Greater falls in blood pressure were produced by haemorrhage of 20-45% of the blood volume, but again the difference in the mean falls before and during jaundice was not significant (P more than 10%).

Severe haemorrhage with hypotension for 90 minutes.

This was studied in 10 dogs. One jaundiced dog died during the period of hypotension and one dog developed a serious cardiac arrhythmia requiring termination of the experiment before satisfactory data could be obtained. In a third dog, complete studies could not be performed, because of clotting of the blood withdrawn.

Inulin and P.A.H. clearance were measured before the 90 minute period of hypotension and 30, 60 and 90 minutes after replacementtransfusion as described in the Appendix, and the results obtained in 7 animals are given in Table 25, page 61. The same procedure was carried out 6 weeks after bile duct ligation. Inulin and P.A.H. clearance following hypotension have been expressed as a percentage of the basal value. Glomerular filtration rate rapidly returned to the basal value following blood replacement, both in jaundiced and non-jaundiced animals. P.A.H. clearance usually returned to values slightly below normal. There was no significant difference in the values obtained in jaundiced and non-jaundiced dogs.

We conclude that in normal dogs following a period of haemorrhage-induced hypotension Inulin clearance rapidly returns to normal and P.A.H. clearance rapidly returns to values only slightly below normal. The presence of jaundice does not alter this pattern of response. Extraction rates for P.AH. were not determined in these dogs and, therefore, it is not possible to state that the low values for P.A.H. clearance represent a failure of effective renal plasma flow to return to normal levels.

There was no evidence of delayed renal damage following the 90 minute period of hypotension in either normal or jaundiced dogs as evidenced by a return of the clearance of Inulin and P.A.H. to pre-hypotension levels, both when measured immediately and after a 7 day interval. In interpreting these findings, it is important to appreciate that the dog's kidney is very resistant to ischaemic damage; acute renal failure following haemorrhagic shock has not been described in dogs (Smith, 1951, Kramer, 1962) and renal artery clamping must be continued for 2-3 hours to produce damage to nephrons. (Van Slyke et al. 1944).

Volume of blood removed to produce hypotension.

The blood volume was measured in all dogs, with and without jaundice, before production of hypotension. The volume of blood, required to be removed to effect hypotension of between 60 and 70 mm. Hg. was expressed as a percentage of the measured blood volume. The results are given in table 26, page 62 and are available for 8 dogs. Less blood had to be removed from the jaundiced dogs to produce hypotension - mean difference 9.8% $\pm$ 3.14. This difference is probably statistically significant (P less than 5% but greater than 1%). The possibility that the increased tendency of jaundiced dogs to develop hypotension on acute blood volume reduction was related to a lower initial blood pressure, or to an initially lower blood volume was considered. Correlation coefficients were calculated between the changes in mean systolic blood pressure in each dog before and during jaundice and the difference in the amount of blood removed to produce hypotension. Similar calculations were made for blood volume changes. No significant correlation could be demonstrated. (P greater than 10% for the former and greater than 5%, but less than 10% for the latter).

Blood Volume Measurements

Blood and plasma volume measurements were carried out under comparable conditions in all dogs before and 4-6 weeks after bile duct ligation. The results are given in Table 27, page 63. Except in the case of the first 3 dogs, all blood volumes were measured after the infusion of 200 ml. of normal saline containing Inulin and P.A.H. As this might obscure changes in plasma volume, both the volume measured and a "corrected value" representing the measured value less an arbitrary 200 ml. are given. The use of either value does not significantly affect the results. Changes in blood and plasma volume in each dog following the production of jaundice are expressed as a percentage of the pre-jaundice value.

Plasma volume was reduced in 12 dogs when jaundiced and increased in 5. The mean difference in the measured volume was $-4.8\% \pm 3.3$ (Table 28, page 64). This difference was not, however, significant (P greater than 0.10). Whole blood volume was likewise reduced in 12 dogs in association with jaundice. The mean difference before and during jaundice was $-7.7\% \pm 2.9$. This value is probably significant (P less than 5%, but greater than 1%) (Table 28). When expressed in ml./kg. body weight, both plasma and whole blood volume showed increases in association with jaundice. In neither instance, however, did this reach the 5% level of significance.

In the interpretation of these results, note must be taken of certain practical aspects of blood volume measurements in the dog. Reeve et al. (1953) studying the distribution of cells and plasma in normal and splenectomised dogs, showed that in the former, body haematocrit estimations can vary following anaesthesia, excitement or adrenaline injection.

This they attributed to addition of red cells to the circulation by contraction of the spleen, the phenomenon not being demonstrated in splenectomised animals. None of our dogs were splenectomised and it was possible, therefore, that variations in body haematocrit could have occurred during the experiments, so leading to false blood volume estimations. However, separate measurements of blood volume at 7-10 day intervals under identical experimental conditions showed excellent agreement. (Table 17)

The second point to note is that all the dogs with jaundice had some degree of splenomegaly. If splenic contraction occurred, during our estimations of blood volume in non-jaundiced dogs, the venous haematocrit would rise. (Reeve et al. 1953) In jaundiced dogs, on the other hand, because of congestive splenomegaly, the same degree of splenic contraction might not be possible and falsely low venous haematocrits would result. In humans, marked splenomegaly is associated with raised body haematocrit: venous haematocrit ratios. (Mollison, 1961) Such a difference in splenic activity in jaundiced dogs would lead to falsely low estimations of whole blood volume. Even if this has occurred to some extent, it would not alter our conclusion that jaundice is not associated with a <u>fall</u> in blood volume, when this is expressed on a body weight basis.

TABLE 1

Case No.	Age (years)	Diagnosis	Duration of jaundice (weeks)	Blood Pressure (mm.Hg.)	Serum Bilirubin (mg./100ml.)	Blood Urea (mg./100ml.)
MALES						
1	66	Ca. of ampulla	4	190/120	8.9	39
2	49	Ca. of pancreas	4	140/90	8.0	41
3	40	Ca. of gallbladder	3	200/100	15.4	48
4	60	Ca. of pancreas	3	140/90	10.8	33
5	60	Ca. of pancreas	3	125/70	9.2	44
6	59	Ca. of pancreas	4	170/110	13.0	35
7	55	Ca. of ampulla	3	110/70	14.1	36
8	54	Ca. of pancreas	4	120/80	12.9	36
9	58	Cholelithiasis	4	140/100	5.0	34
10	57	Cholelithiasis	4	140/80	5.0	32
11	58	Ca. of pancreas	3	130/90	6.7	33
12	62	Ca. of gallbladder	5	160/110	7.6	42
13.	62	Ca. of pancreas	5	130/80	16.8	39
14	49	Cholelithiasis	2	165/95	12.8	38
15	60	Ca. of pancreas	5	175/105	25.0	36
16	57	Cholelithiasis	8	160/100	7.4	41
MEAN	56.6		4.0		11.2	37.9
FEMALES						
17	49	Cholelithiasis	3	180/100	10.3	29
18	62	Ca. of ampulla	4	120/70	6.6	27
19	59	Ca. of hepatic ducts	12	135/80	14.2	40
20	65	Intra hepatic cholestasis	12	140/80	10.2	38
21	65	Ca. of pancreas	4	140/90	12.1	38
22	64	Cholelithiasis	3	145/95	9.2	39
23	52	Ca. of gallbladder	8	130/85	18.0	24
24	39	Stricture of common duct	3	140/80	6.0	42
25	50	Cholelithiasis	2	150/85	20.0	36
MEAN	56.1		5.7		11.8	34.8

Summary of cases studied with salient clinical and biochemical findings.

TABLE 2

Case	Age (years)	Diagnosis	Serum Bilirubin (mg./100ml.)	Blood Urea (mg./100ml.)	Protein-uria	Post-op. course
MALES						
D.A.	54	Ca. of pancreas	11.9	37	0	Normal
S.C.	51	Cholelithiasis	8.0	--	0	Normal
J.H.	49	Ca. of bile duct	17.3	36	0	Normal
E.J.(29)	61	Ca. of pancreas	5.5	--	0	Renal failure
A.K.	49	Cholelithiasis	6.8	33	0	Normal
M.K.	58	Ca. of pancreas	7.3	--	0	Normal
W.L.(30)	64	Cas. of pancreas	16.1	25	0	Renal failure
G.M.	65	Cholelithiasis	11.4	35	0	Normal
J.R.	61	Cholelithiasis	5.8	--	--	Normal
C.S.	65	Ca. of pancreas	12.0	--	0	Normal
FEMALES						
M.D.	59	Ca. of pancreas	14.0	--	0	Normal
E.W.	34	Cholelithiasis Pyelonephritis	9.8	--	+	Normal

Summary of patients admitted to hospital with obstructive jaundice between September, 1960 and June, 1963, who were not included in the study.

Figures in parenthesis refer to the case abstracts (Appendix 1).

TABLE 3

Case	Age (years)	Sex	Diagnosis
F.L. (27)	69	F	Cholecystitis; no previous operation
G.W. (26)	65	F	Cholelithiasis; no previous operation
J.L. (28)	40	M	Intrahepatic obstruction; renal failure followed laparotomy

Summary of patients admitted to hospital with obstructive jaundice and renal failure already established. Figures in parenthesis refer to case abstracts (Appendix 1).

TABLE 4

Case No.	Age (years)	Serum Bilirubin mg./100ml.
MALES		
1	66	8.9
2	49	8.0
3	40	15.4
4	60	10.8
5	60	9.2
6	59	13.0
7	55	14.1
8	54	12.9
9	58	5.0
10	57	5.0
11	58	6.7
12	62	7.6
13	62	16.8
14	49	12.8
15	60	25.0
16	57	7.4
FEMALES		
17	49	10.3
18	62	6.6
19	59	14.2
20	65	10.2
21	65	12.1
22	64	9.2
23	52	18.0
24	39	6.0
25	50	20.0

Summary of renal clear
values are corrected t
values (see text).

TABLE 5

Renal Clearance	Subjects	Mean value ± S.E. (ml./min.)	Significance of Difference
	MALES		
Inulin	Jaundice (12)	101.8 ± 4.9	$0.001 < P < 0.01$
	Normal (34)	124.1 ± 4.4	
	FEMALES		
	Jaundice (8)	98.9 ± 4.9	$0.10 > P > 0.05$
	Normal (16)	108.8 ± 3.4	
	MALES		
P.A.H.	Jaundice (12)	454.7 ± 34.4	$0.001 < P < 0.01$
	Normal (30)	654.0 ± 29.7	
	FEMALES		
	Jaundice (8)	478.9 ± 31.7	$0.10 > P > 0.05$
	Normal (11)	592.0 ± 46.1	
	MALES		
Filtration Fraction	Jaundice (12)	0.23 ± 0.009	$P < 0.001$
	Normal (31)	0.19 ± 0.006	
	FEMALES		
	Jaundice (8)	0.21 ± 0.009	$0.10 > P > 0.05$
	Normal (11)	0.19 ± 0.012	

Clearance values obtained in jaundiced patients compared with the normal values of Smith (1951). Numbers in parenthesis refer to the number of subjects studied.

TABLE 6

Endogenous Creatinine Clearance

Subjects	Mean Value ± S.E. (ml./min.)	Significance of Difference
MALES		
Jaundice (16)	102.2 ± 3.6	$0.05 > P > 0.01$
Normal (8)	116.0 ± 3.8	
FEMALES		
Jaundice (9)	103.2 ± 5.5	$0.10 > P > 0.05$
Normal (11)	107.0 ± 4.2	

Results obtained for creatinine clearances in 25 patients with obstructive jaundice compared with normal values. Numbers in parenthesis refer to the number of subjects studied.

TABLE 7

Case No.	Age (years)	Diagnosis	Endogenous Creatinine Clearance Pre-operative (ml./min.)	Post-Operative (ml./min.)	Difference %
3	40	Ca. of gallbladder	84	90	+7
4	60	Ca. of pancreas	110	86	-22
5	60	Ca. of pancreas	84	78	-7
7	59	Ca. of ampulla	110	100	-9
8	54	Ca. of pancreas	115	94	-18
10	57	Cholelithiasis	98	82	-16
11	58	Ca. of pancreas	97	80	-18
12	62	Ca. of gallbladder	77	81	+5
14	49	Cholelithiasis	110	92	-16
17	49	Cholelithiasis	128	118	-8
19	59	Ca. of hepatic ducts	86	94	+9
20	65	Cholelithiasis	78	84	+8
21	65	Ca. of pancreas	116	102	-12
22	64	Cholelithiasis	105	110	+5
23	52	Ca. of gallbladder	109	100	-8
MEAN	56.9		100.5		-6.7 ± 3.8

Results of endogenous creatinine clearance determinations before and 7-9 days after operation in 15 patients with obstructive jaundice.

TABLE 8

Case	Age (years)	Operation	Endogenous Creatinine Clearance Pre-operative (ml./min.)	Post-operative (ml./min.)	Difference %
A.R.	54	Cholecystectomy	117	113	-3
J.D.	43	Cholecystectomy	117	122	+4
E.B.	60	Cholecystectomy	98	86	-12
W.F.	62	Cholecystectomy	104	103	-1
A.M.	48	Cholecystectomy	107	96	-10
M.C.	55	Cholecystectomy	128	113	-13
R.D.	54	Cholecystectomy	104	79	-24
C.Y.	40	Cholecystectomy	110	113	+3
A.W.	67	Cholecystectomy	76	87	+14
F.O'H.	41	Cholecystectomy	122	102	-16
T.Y.	59	Cholecystectomy	115	126	+10
A.C.	64	Cholecystectomy	65	45	-30
L.H.	54	Cholecystectomy	77	57	-26
W.V.	65	Cholecystectomy	101	88	-13
J.L.	52	Cholecystectomy	109	94	-14
T.D.	62	Cholecystectomy	84	90	+7
E.C.	50	Cholecystectomy	122	109	-11
J.F.	55	Partial gastrectomy	107	94	-12
R.C.	49	Partial gastrectomy	96	90	-6
K.B.	41	Partial gastrectomy	132	126	-5
E.H.	47	Partial gastrectomy	124	116	-6
R.B.	53	Partial gastrectomy	106	102	-4
MEAN	53.4		105.5		-7.6 ± 2.40

Results of endogenous creatinine clearances performed before and 7-10 days after operation on 22 non-jaundiced patients.

TABLE 9

Case No.	Age (years)	Serum Bilirubin mg/100ml.	Blood Urea mg/100ml.	URINE INVESTIGATIONS Protein mg/24 hr.	Sugar	Amino acid Pattern	Max. Osmolality m.osmol/Kg.	Minimum pH.	Minimum Na. Excretion (m.eq/24hr.)	Full Recovery	Necropsy
MALES											
1	66	8.9	39	0	0	---	902	5.01	--	0	Tubular Necrosis
2	49	8.0	41	300	0	---	814	4.94	--	0	0
3	40	15.4	48	0	0	Normal	960	5.36	--	0	0
4	60	10.8	33	0	0	Normal	960	5.36	--	0	0
5	60	9.2	44	200	0	Normal	780	5.42	--	0	Nephrosclerosis
6	59	13.0	35	0	0	---	890	5.26	--	0	0
7	55	14.1	36	0	+	Normal	1020	5.59	16	0	Tubular Necrosis
8	54	12.9	36	0	+	Normal	824	5.22	--	0	-
9	58	5.0	34	0	0	Normal	1020	4.78	--	+	-
10	57	5.0	32	500	0	---	964	5.12	14	+	-
11	58	6.7	33	0	+	---	1010	5.33	--	0	0
12	62	7.6	42	0	0	---	984	5.58	15	0	0
13	62	16.8	39	0	0	---	879	5.20	--	0	0
14	49	12.8	38	0	0	Normal	986	--	--	+	-
15	60	25.0	36	200	0	Normal	1000	5.30	11	0	0
16	57	7.4	41	0	0	Normal	1012	5.40	--	+	-
FEMALES											
17	49	10.3	29	0	0	Normal	1024	5.00	17	+	-
18	62	6.6	27	0	0	Normal	864	--	--	+	-
19	59	14.2	40	800	0	---	876	5.26	18	+	-
20	65	10.2	38	0	0	---	840	5.40	14	0	Nephrosclerosis
21	65	12.1	38	0	0	---	922	5.08	21	0	0
22	64	9.2	39	0	0	---	867	5.77	--	+	-
23	52	18.0	24	0	0	Normal	942	**	**	0	0
24	39	6.0	42	0	0	Normal	978	5.20	18	+	-
25	50	20.0	36	0	0	Normal	962	5.26	--	+	-

Summary of the results of urine tests in 25 patients with obstructive jaundice.

TABLE 10

Case No.	CREATININE Clearance ml./min.	BLOOD Urea mg./100 ml.	BLOOD HCO_3^- m.eq./l.	BLOOD CL^- m.eq./l.	BLOOD K^+ m.eq./l.	URINE Minimum pH	URINE Titratable Acidity µ.eq./min.	URINE NH_4^+ µ.eq./min.	URINE Total H^+ µ.eq./min.	URINE Urine flow ml./min.
2	103	41	25	104	4.6	4.94	37	108	145	4.6
3	84	48	22	107	5.2	5.36	29	84	113	1.9
5	84	44	32	101	3.8	5.42	28	71	99	1.3
6	110	35	28	102	4.3	5.59	26	94	120	3.9
8	115	36	28	98	4.5	5.12	24	66	90	5.6
9	120	34	31	101	3.7	4.78	33	74	107	2.1
11	97	33	23	101	4.5	5.33	28	100	128	2.4
12	77	42	26	103	4.0	5.58	25	68	93	1.3
16	124	41	28	95	4.0	5.40	27	71	98	2.1
17	128	29	30	99	4.1	5.00	38	83	121	2.6
19	86	40	34	101	3.9	5.26	24	79	103	1.4
20	78	38	27	100	4.3	5.40	29	67	96	0.9
21	116	38	31	99	3.9	5.08	33	95	128	2.0
22	105	39	25	102	4.3	5.77	20	78	98	0.7
24	114	42	25	109	4.1	5.20	27	80	107	0.9
25	100	36	32	93	4.0	5.26	30	91	121	1.9
NORMAL VALUES:		15-45	23-31	92-107	3.5-5.3	4.60-4.92	23-49	30-81	64-130	

Results obtained following an acid load in 16 patients with obstructive jaundice.

Blood values on these obtained on a separate occasion.

TABLE 11

Case No.	Creatinine Clearance (ml./min.)	Urine: Minimum pH.	Urine: Titratable Acidity (μ.eq./min.)	Urine: NH_4 (μ.eq./min)	Urine: Total H^+ (μ.eq./min)	Urine: Urine Flow (ml./min.)
9	124	4.61	48	68	116	1.9
17	126	4.70	39	55	94	2.1
22	103	5.10	51	47	98	1.2
24	---	4.82	43	49	92	1.0

Results obtained following an acid load in 4 patients studied 2-4 months after relief of jaundice.

TABLE 12

Case No.	Age (years)	Sex	Diagnosis	Blood Urea (mg./100 ml.)	24-hr. Urine Sodium Excretion (m.eq.)
			Jaundiced Subjects		
7	55	M	Ca. of ampulla	36	16
10	57	M	Cholelithiasis	32	14
12	62	M	Ca. of gallbladder	42	15
17	49	F	Cholelithiasis	29	17
19	59	F	Ca. of hepatic ducts	40	18
20	65	F	Intrahepatic cholestasis	38	14
21	65	F	Ca. of pancreas	38	21
23	52	F	Ca. of gallbladder	24	11
24	39	F	Stricture common bile duct	42	18
MEAN	56			36	16
			Controls		
J.R.	29	M	Spont. pneumothorax	29	15
A.F.	35	F	Anaemia	34	16
G.B.	60	M	Bronchitis	41	12
E.K.	55	F	Bronchitis	42	17
R.S.	62	F	Ca. of breast	37	10
W.S.	49	M	Ca. of stomach	40	14
D.R.	57	M	Ca. of colon	34	16
MEAN	50			37	14

Minimum 24-hour excretion of sodium in the urine following 3 days' administration of 4 mg. 9 - α - fluorohydrocortisone per day in 9 jaundiced and 7 control subjects.

TABLE 13

Case No.	Venous Haematocrit	Body Haematocrit	Plasma Volume (mls) Measured	Plasma Volume (mls) Expected*	Δ%	Blood Volume (mls) Measured	Blood Volume (mls) Expected*	Δ%
MALES								
1	41.4	37.7	2997	2770	+8.2	4810	4770	+0.8
2	42.3	38.5	2880	2630	+9.5	4690	4520	+3.8
3	45.1	41.0	2580	2460	+4.9	4370	4230	+3.3
4	44.8	40.8	2530	2510	+0.8	4270	4310	-0.9
7	36.8	33.5	3000	2440	+23.0	4510	4200	+7.4
8	44.7	40.7	2860	2850	+0.4	4830	4900	-1.4
12	42.6	38.8	2910	2580	+12.8	4710	4440	+6.1
13	40.9	37.2	3110	2650	+17.4	4960	4550	+9.0
FEMALES								
19	42.1	38.3	2370	2490	-4.8	3840	3910	-1.8
20	38.2	34.8	2590	2380	+8.8	3980	3750	+6.1
21	37.8	34.4	3080	2760	+11.6	4700	4340	+8.3
22	37.0	33.7	4380	3510	+24.8	6610	5520	+19.7
24	40.6	36.9	2160	2300	-6.1	3420	3620	-5.5
25	42.2	38.4	2930	2870	+2.1	4750	4520	+5.1

Haematocrit, plasma and blood volume measurements in 14 patients with obstructive jaundice.

*"Expected" values derived from surface area measurements (Appendix 2)

Δ% Difference between measured and expected volumes expressed as a percentage of the latter.

TABLE 14

	No. of observations	Mean Difference ± S.E. (%)	Significance of Difference
Plasma volume	14	+8.1 ± 2.5	$0.001 < P < 0.01$
Blood volume	14	+4.3 ± 1.7	$0.05 > P > 0.01$

Statistical analysis of the difference between measured and expected plasma and blood volumes where the difference is expressed as a percentage of the expected value.

TABLE 15

Dog No.	Serum Bilirubin mg./100ml.	Weight (kg)			Inulin Clearance (ml/min)			P.A.H. Clearance (ml/min)		
		Control	Jaundice	Δ%	Control	Jaundice	Δ%	Control	Jaundice	Δ%
1	10.5	15.5	13.2	-15	95	60	-37	233	166	-29
2	18.6	16.4	14.1	-14	89	56	-37	219	219	0
3	8.2	24.6	19.1	-22	80	99	+24	277	293	+6
4	7.7	18.7	16.8	-10	75	90	+20	211	273	+29
5	7.1	13.6	12.2	-10	66	51	-38	162	175	+8
6	6.0	19.8	16.8	-15	82	60	-27	199	122	-39
8	9.8	8.0	7.7	-4	51	34	-33	121	78	-36
9	5.6	22.3	17.2	-23	62	71	+15	222	197	-11
10	8.5	14.1	12.7	-10	66	45	-32	133	130	-2
11	6.4	17.3	15.5	-10	77	74	-4	199	183	-8
13	18.0	13.9	10.5	-24	45	16	-64	104	54	-48
15	18.0	12.2	9.3	-24	41	32	-22	102	84	-18
16	4.5	25.4	19.5	-23	90	91	+1	267	301	+13
17	12.8	13.9	10.9	-22	55	30	-46	132	90	-32
18	10.8	11.8	10.9	-8	48	30	-38	146	85	-42
19	7.5	14.6	12.5	-14	80	68	-15	208	239	+15
20	8.0	14.1	10.9	-23	60	59	-2	150	117	-22

Dog No.	Renal Blood Flow (ml/min)			Filtration Fraction			Mean Systolic Blood Pressure (mm.Hg)		
	Control	Jaundice	Δ%	Control	Jaundice	Δ%	Control	Jaundice	Δ%
1	409	274	-33	0.408	0.362	-11	170	115	-32
2	377	373	-1	0.406	0.256	-37	104	118	+13
3	486	486	0	0.289	0.338	+17	132	123	-7
4	340	473	+39	0.355	0.330	-7	156	168	+8
5	221	219	-1	0.408	0.292	-28	110	56	-49
6	309	179	-42	0.412	0.492	+19	142	122	-14
8	176	128	-27	0.421	0.436	+4	136	122	-10
9	345	340	-2	0.279	0.361	+29	120	150	+25
10	204	201	-2	0.496	0.346	-30	155	149	-4
11	351	337	-4	0.387	0.404	+4	168	172	+2
13	184	86	-53	0.433	0.296	-32	138	118	-14
15	170	121	-29	0.402	0.381	-5	138	130	-6
16	451	431	-4	0.337	0.303	-10	140	126	-10
17	239	155	-35	0.417	0.333	-20	150	140	-7
18	236	137	-42	0.329	0.353	+7	140	142	+1
19	356	431	+21	0.370	0.280	-30	160	132	-18
20	249	183	-26	0.400	0.500	+25	154	125	-19

Weight, renal clearances and blood pressure before and after production of jaundice in 17 dogs. The serum bilirubin level indicates the degree of jaundice at the time of the investigation.

Δ% = Difference in clearance values before and with jaundice expressed as a percentage of the former.

TABLE 16

Observation	Mean Difference ± S.E.	Significance of Difference
Serum Bilirubin	+ 9.9 mg./100 ml. ± 1.08	$P < 0.001$
Weight	-15.9% ± 1.62	$P < 0.001$
Mean Systolic Blood Pressure	-8.3% ± 4.09	$0.10 > P > 0.05$
Venous haematocrit	-2.4% ± 4.0	$P > 0.10$
Plasma volume	-4.8% ± 3.3	$P > 0.10$
Blood volume	-7.7% ± 2.9	$0.10 > P > 0.05$

Statistical analysis of the difference in the values obtained in 17 dogs before and after production of jaundice. Differences in these values in individual dogs were expressed as a percentage of the initial value and the percentage differences meaned for group as a whole.

TABLE 17

CONTROL

Dog No.	C. In. First	C. In. Second	C. In. Δ%	C. PAH First	C. PAH Second	C. PAH Δ%	R.B.F. First	R.B.F. Second	R.B.F. Δ%	F.F. First	F.F. Second	F.F. Δ%	BLOOD VOLUME First	BLOOD VOLUME Second	BLOOD VOLUME Δ%
1	95	89	-6	233	218	-6	409	387	-5	0.41	0.41	0	1695	1650	-3
2	89	94	-6	219	223	+2	377	384	+2	0.41	0.42	+2	2560	2460	-4
3	80	87	+9	277	291	+5	486	512	+5	0.29	0.30	+3	2647	2720	+3
4	75	83	+11	211	228	+8	340	364	+7	0.36	0.36	0	1610	1580	-2
11	77	71	-8	199	186	-7	351	334	-5	0.39	0.38	-3	1560	1500	-4
13	45	51	+13	104	114	+10	184	208	+13	0.43	0.45	+5	1235	1340	+9
15	41	46	+12	102	112	+10	170	185	+9	0.40	0.39	-3	1340	1305	-3
16	90	82	-9	267	248	-7	451	410	-9	0.34	0.33	-3	2460	2490	+1
17	55	62	+13	132	144	+6	239	260	+9	0.42	0.43	+2	1450	1500	+3
18	48	52	+8	146	151	+3	236	248	+5	0.33	0.34	+3	1345	1420	+6

JAUNDICE

Dog No.	C. In. First	C. In. Second	C. In. Δ%	C. PAH First	C. PAH Second	C. PAH Δ%	R.B.F. First	R.B.F. Second	R.B.F. Δ%	F.F. First	F.F. Second	F.F. Δ%	BLOOD VOLUME First	BLOOD VOLUME Second	BLOOD VOLUME Δ%
1	60	65	+8	166	174	+5	274	280	+2	0.36	0.38	+6	1185	1207	+2
2	56	51	-9	219	198	-10	373	324	-13	0.26	0.26	0	1920	1840	-4
3	99	91	-8	293	281	-4	486	470	-3	0.34	0.32	+6	2270	2310	+2
4	90	86	-4	273	256	-6	473	448	-5	0.33	0.34	+3	1705	1770	+4
6	60	60	0	122	128	+5	179	184	+3	0.49	0.47	-4	1550	1650	+6
11	74	82	+11	183	195	+7	337	358	+6	0.40	0.42	+5	2270	2310	+2
13	16	13	-19	54	48	-11	86	81	-6	0.30	0.27	-10	1290	1260	-2
15	32	34	+6	84	86	+2	121	129	+7	0.38	0.40	+5	2190	2000	-9
17	30	29	-3	90	84	-7	155	146	-6	0.33	0.35	+6	1170	1200	+3

Results of renal clearance and blood volume estimations on control and jaundiced dogs carried out on two separate occasions on the same animal at intervals of 7-10 days.

C. In. = Inulin clearance. C. PAH = Para-amino hippurate clearance. R.B.F. = Calculated renal blood flow. F.F. = Ratio C.In./C. PAH = Filtration fraction. Δ% = Difference between the first and second values obtained expressed as a percentage of the first.

TABLE 18

	Mean Difference ± S.E.	Significance of Difference
Inulin Clearance	-19.7 ± 6.07	$0.001 < P < 0.01$
P.A.H. Clearance	-12.7 ± 5.53	$0.01 < P < 0.05$
Renal Blood Flow	-14.2 ± 5.92	$0.01 < P < 0.05$
Filtration Fraction	-6.2 ± 5.1	$0.01 < P > 0.10$

Statistical analysis of the difference in renal clearances in 17 dogs following production of jaundice. The values obtained in individual dogs when jaundiced were expressed as a percentage of the initial value for that dog and these percentage differences meaned for the group as a whole.

TABLE 19

	C. In.	C. P.A.H.	R.B.F.	F.F.
Serum bilirubin	-0.590*	-0.376	-0.406	-0.467
Weight	-0.169	+0.076	+0.232	-0.166
Mean systolic blood pressure	+0.384	+0.084	+0.132	+0.268
Venous haematocrit	+0.291	+0.164	+0.256	+0.238
Plasma volume	+0.064	+0.199	+0.079	-0.270
Blood volume	+0.245	+0.329	+0.368	-0.069

Correlation co-efficients between changes in renal clearances and changes in other parameters in 17 dogs following production of obstructive jaundice.

All control values for serum bilirubin were between 0.1 and 0.4 mg./100 ml. and for simplicity this has been taken as zero. The change in all other parameters is calculated as a percentage of the control values.

*The only instance in which significant correlation has been demonstrated.

TABLE 20

Dog. No.	Normal C. In. ml/min	Normal C. PAH ml/min	Normal R.B.F. ml/min	Jaundiced C. In. ml/min	Jaundiced C. PAH ml/min	Jaundiced R.B.F ml/min	Jaundice relieved C. In. ml/min	Jaundice relieved C. PAH ml/min	Jaundice relieved R.B.F. ml/min
1	95	233	409	60	166	274	85	228	394
6	82	199	309	60	122	179	81	180	275
19	80	208	356	68	239	431	80	266	416
20	60	150	249	59	117	183	64	162	251

Results of renal clearances performed on 4 dogs before, during and after jaundice.

INULIN CLEARANCE

Dog No.	CONTROL Basal ml/min	CONTROL Mild Haemorrhage ml/min	Δ%(A)	JAUNDICE Basal	JAUNDICE Mild Haemorrhage ml/min	Δ%(B)	Difference in Response (A-B)	CONTROL Basal	CONTROL Moderate Haemorrhage ml/min	Δ%(C)	JAUNDICE Basal	JAUNDICE Moderate Haemorrhage ml/min	Δ%(D)	Difference in Response (C-D)
1	95	99	+4	60	56	-7	+11	95	72	-24	60	53	-12	-12
2	89	99	+11	56	51	-9	+20	89	93	+4	56	55	-2	+6
3	80	74	-8	99	98	-1	-7	80	74	-8	99	98	-1	-7
4	75	76	+1	90	92	+20	-1	75	74	-1	90	76	-16	+15
6	82	63	-23	60	48	-20	-3	82	60	-27	60	40	-33	+6
8	51	50	-2	34	40	+18	-20	51	55	+8	34	36	+6	+2
9	62	59	-5	71	67	-6	+1	62	66	+6	71	62	-13	+19
10	66	52	-21	45	36	-20	-1	66	46	-30	45	33	-27	-3
MEAN			-5.4			-5.4	0			-9			-12.3	+3.3±3.7

P.A.H. CLEARANCE

Dog No.	CONTROL Basal ml/min	CONTROL Mild Haemorrhage ml/min	Δ%(A)	JAUNDICE Basal	JAUNDICE Mild Haemorrhage ml/min	Δ%(B)	Difference in Response (A-B)	CONTROL Basal	CONTROL Moderate Haemorrhage ml/min	Δ%(C)	JAUNDICE Basal	JAUNDICE Moderate Haemorrhage ml/min	Δ%(D)	Difference in Response (C-D)
1	233	218	-6	166	164	-1	-5	233	212	-9	166	158	-5	-4
2	219	288	+32	219	218	0	+32	219	294	+34	219	222	-1	+35
3	277	233	-16	293	285	-3	-13	277	256	-8	293	278	-5	-3
4	211	185	-12	273	230	-2	-10	211	188	-11	273	227	-17	+6
6	199	152	-24	122	116	+49	+25	199	128	-36	122	94	-23	-13
8	121	108	-11	78	80	+3	-14	121	104	-14	78	78	0	-14
9	222	198	-11	197	177	-10	-1	222	166	-25	197	152	-23	-2
10	133	127	-5	130	98	-25	+20	133	99	-26	130	93	-29	+3
MEAN			-6.6			-10.9	+4.3±6.6			-11.9			-12.9	+0.9±4.0

TABLE 21 (ctd.)

RENAL BLOOD FLOW

Dog No.	CONTROL Basal ml/min	CONTROL Mild Haemorrhage ml/min	Δ%(A)	JAUNDICE Basal	JAUNDICE Mild Haemorrhage ml/min	Δ%(B)	Difference in Response (A-B)
1	409	384	-6	274	282	+3	-9
2	377	495	+31	373	344	-8	+39
3	486	379	-22	486	473	-3	-19
4	340	320	-6	473	401	-15	+9
6	309	235	-24	179	183	+2	-26
8	176	151	-14	128	124	-3	-11
9	345	320	-7	340	308	-9	+2
10	204	299	+3	201	153	-24	+27
MEAN			-5.6			-7.1	+1.6±8.0

Dog No.	CONTROL Basal ml/min	CONTROL Moderate Haemorrhage ml/min	Δ%(C)	JAUNDICE Basal ml/min	JAUNDICE Moderate Haemorrhage ml/min	Δ%(D)	Difference in Response (C-D)
1	409	357	-13	274	259	-6	-7
2	377	480	+27	373	331	-11	+38
3	486	400	-18	486	448	-8	-10
4	340	305	-10	473	349	-26	+16
6	309	204	-34	179	142	-21	-13
8	176	143	-19	128	115	-10	-9
9	345	286	-17	340	246	-28	+11
10	204	158	-23	201	164	-18	-5
MEAN			-13.4			-16	+2.6±6.3

MEAN SYSTOLIC BLOOD PRESSURE

Dog No.	CONTROL Basal mm/Hg	CONTROL Mild Haemorrhage mmHg.	Δ%(A)	JAUNDICE Basal mmHg.	JAUNDICE Mild Haemorrhage mmHg.	Δ%(B)	Difference in Response (A-B)
1	170	170	0	115	110	-4	+4
2	154	157	+2	118	106	-10	+12
3	132	128	-3	123	119	-3	0
4	168	160	-5	156	154	-1	-4
6	142	137	-4	122	115	-6	+2
8	136	134	-2	122	117	-4	+2
9	130	133	+2	150	140	-7	+9
10	155	155	0	149	133	-11	+11
MEAN			-1.3			-5.8	+4.5±2.0

Dog No.	CONTROL Basal mmHg.	CONTROL Moderate Haemorrhage mmHg.	Δ%(C)	JAUNDICE Basal mmHg.	JAUNDICE Moderate Haemorrhage mmHg.	Δ%(D)	Difference in Response (C-D)
1	170	160	-6	115	103	-10	+4
2	154	160	+4	118	89	-25	+29
3	132	124	-6	123	112	-10	+4
4	168	157	-5	156	150	-4	-1
6	142	113	-20	122	97	-26	+6
8	136	131	-4	122	111	-9	+5
9	130	120	-8	150	110	-27	+19
10	155	111	-28	149	118	-21	-7
MEAN			-9.1			-16.5	+7.4±4.1

Results obtained for renal clearances and mean systolic blood pressure following mild and moderate hemorrhage in 8 dogs before and with obstructive jaundice.

Δ% = Difference between basal and second value expressed as a percentage of the basal.

TABLE 22

Blood removed expressed as a % of initial blood volume.

Dog No.	Mild Haemorrhage		Moderate Haemorrhage	
	Control	Jaundice	Control	Jaundice
1	12	17	24	34
2	12	16	24	32
3	13	13	25	26
4	16	18	33	35
6	20	23	40	45
8	16	16	32	30
9	21	20	49	44
10	14	9	20	12
MEAN	15.5	16.5	30.9	32.3

TABLE 23

	Mild Haemorrhage		Moderate Haemorrhage	
	Mean of Differences $\pm$ S.E.	Significance	Mean of Differences $\pm$ S.E.	Significance
Inulin Clearance	0	-	$+3.3\pm3.7$	$P > 0.10$
P.A.H. Clearance	$+4.3\pm6.6$	$P > 0.10$	$+0.9\pm4.0$	$P > 0.10$
Renal blood flow	$+1.6\pm8.0$	$P > 0.10$	$+2.6\pm6.3$	$P > 0.10$

Statistical analysis of the changes observed in renal clearances following mild and moderate haemorrhage in 8 dogs before jaundice compared with the changes observed during jaundice. For explanation of calculations see text.

TABLE 24

	Changes in Systolic Blood Pressure	
	Mean of Differences ± S.E.	Significance
Mild Haemorrhage	+4.5% ± 2.0	$0.10 > P > 0.05$
Moderate Haemorrhage	+7.4% ± 4.1	$P > 0.10$

Statistical analysis of difference in the response of the mean systolic blood pressure to mild and moderate haemorrhage in 8 dogs with and without jaundice. The change in blood pressure in each dog following haemorrhage was expressed as a percentage of the initial value. This was then compared with the changes observed in the same dog when jaundiced. The values given are the means of the differences for the group as a whole. Positive signs indicate a greater fall in pressure in jaundiced dogs (see text).

TABLE 25

Dog No.	Normal: Basal Clearance ml/min.	Normal: Clearance as % of Basal +30min.	+60min.	+90min.	Jaundiced: Basal Clearance ml/min.	Jaundiced: Clearance as % of Basal +30min.	+60min.	+90min.
				Inulin				
11	77	104	84	91	74	108	93	104
13	45	90	94	98	16	97	97	100
15	41	100	98	106	32	100	125	120
16	90	113	86	111	91	112	120	117
17	55				30	83	107	91
18	48	102	100		30	93	120	103
19	80	91	110	104	68	105	94	98
				P.A.H.				
11	199	89	72	84	183	92	86	90
13	104	84	84	92	54	92	83	74
15	102	78	82	81	84	96	101	94
16	267	92	97	99	301	98	94	89
17	132				90	86	90	84
18	146	93	97	100	85	96	104	106
19	208	84	92	90	239	94	96	99

Inulin and P.A.H. clearance values obtained before and 30, 60 and 90 minutes after a 90 minute period of hypotension (60-70 mm.Hg.).

TABLE 26

Dog. No.	Normal: Basal Blood Pressure (mm. Hg.)	Normal: Blood Volume (mls.)	Normal: Blood Removed (%Blood Volume)	Jaundiced: Basal Blood Pressure (mm.Hg.)	Jaundiced: Blood Volume (mls.)	Jaundiced: Blood Removed (%Blood Volume)	Difference
11	168	1560	51	172	1490	49	-2
13	138	1235	52	118	1190	45	-7
15	138	1340	53	130	1290	31	-22
16	140	2460	49	126	2190	38	-11
17	150	1450	52	140	1170	33	-19
18	140	1350	45	142	1250	43	-2
19	160	1080	52	132	1300	54	+2
20	154	1270	47	125	992	30	-17
MEAN			50.1			40.4	-9.8 ± 3.1-14

Details of blood removed to effect hypotension of between 60 and 70 mm.Hg. in 8 dogs before and after production of jaundice.

TABLE 27

Dog. No.	Serum Bilirubin mg/100ml	Weight (kg.)			Venous Haematocrit			Plasma Volume (ml.)			Corrected Plasma Volume (ml.)			Blood Volume (ml.)			Corrected Blood Volume		
		Control	Jaundice	Δ%	Control	Jaundice	Δ%	Control	Jaundice	Δ%	Control	Jaundice	Δ%	Control	Jaundice	Δ%	Control	Jaundice	Δ%
1	10.5	15.5	13.2	-15	53.1	50.1	-5.7	795	596	-25	795	596	-25	1695	1195	-30	1695	1195	-30
2	18.6	16.4	14.1	-14	49.3	48.7	-1.2	1298	985	-24	1298	985	-24	2501	1920	-23	2501	1920	-23
3	8.2	24.6	19.1	-22	48.9	48.0	-1.8	1295	1180	-9	1295	1180	-9	2560	2270	-11	2560	2270	-11
4	7.7	18.7	16.8	-10	53.9	51.8	-3.9	740	823	+11	540	623	+15	1610	1705	+6	1410	1505	+7
5	7.1	13.8	12.2	-10	26.9	19.3	-28.3	920	894	-3	720	694	-4	1260	1108	-12	1060	908	-14
6	6.0	19.8	16.8	-15	38.6	33.5	-13.2	1075	1030	-4	875	830	-5	1755	1550	-12	1555	1350	-13
8	9.8	8.0	7.7	-4	34.9	42.9	+22.9	618	551	-11	418	351	-16	950	967	+2	750	767	+2
9	5.6	22.3	17.2	-23	37.7	45.9	+17.9	1210	1060	-12	1010	860	-15	1940	1960	+1	1740	1760	+1
10	8.5	14.1	12.7	-10	40.3	39.0	-3.2	880	895	+2	680	695	+2	1465	1460	0	1265	1260	0
11	6.4	17.3	15.5	-10	45.5	44.1	-3.1	850	832	-2	650	632	-3	1560	1490	-4	1360	1290	-5
13	18.0	13.9	10.5	-24	48.7	40.7	-16.4	634	708	+12	434	508	+17	1235	1190	-4	1035	990	-4
15	18.0	12.2	9.3	-24	44.6	33.4	-25.1	745	859	+15	545	659	+21	1340	1290	-4	1140	1090	-4
16	4.5	25.4	19.5	-23	36.5	50.5	+38.4	1300	1085	-17	1100	885	-20	2460	2190	-11	2260	1990	-12
17	12.8	13.9	10.9	-22	51.5	46.5	-9.7	704	628	-11	504	428	-15	1450	1170	-19	1250	970	-22
18	10.8	11.8	10.9	-8	40.9	41.5	+1.5	798	730	-9	598	530	-11	1350	1250	-7	1150	1050	-9
19	7.5	14.6	12.5	-14	45.0	44.5	-1.1	595	726	+22	395	426	+33	1080	1300	+20	880	1100	+25
20	8.0	14.1	10.9	-23	43.7	39.7	-9.2	718	598	-17	518	398	-23	1270	992	-22	1070	792	-26
MEAN				-15.9±1.6			-2.4±4.0			-4.8±3.3			-4.8±4.2			-7.7±2.9			-8.1±3.3

Results obtained for weight, venous haematocrit, plasma and blood volume in 17 dogs before and after production of jaundice.

TABLE 28

	Mean Difference % ± S.E.	Significance of Difference
Plasma volume (mls.)	- 4.8 ± 3.3	P > 0.10
"Corrected" plasma volume (mls.)	- 4.8 ± 4.2	P > 0.10
Plasma volume ml./kg. body weight	+ 3.8 ±2.2	P > 0.10
Blood volume (mls.)	- 7.7 ± 2.9	0.01 < P < 0.5
"Corrected" blood volume (mls.)	-8.1 ± 3.3	0.01 < P < 0.5
Blood volume ml./kg. body weight	+ 6.2 ± 3.3	0.10 > P > 0.5

Statistical analysis of plasma and blood volume changes in 17 dogs with obstructive jaundice. For method of calculation see text.

DISCUSSION

Pathological changes in the kidneys of patients with obstructive jaundice have been recognised for over a century, (Frerichs, 1858, Legg, 1880, Quincke, 1884 and Werner, 1887) and an association between liver disease and kidney dysfunction was described by Austin Flint in 1863. The development of renal failure in patients with obstructive jaundice, who had undergone surgery was also recognised in the nineteenth century (Quincke, 1899) and illustrative cases were reported by Clairmont and Haberer in 1911. Little attention appears to have been given to these reports, however, until interest in the subject was revived by the publication in the nineteen twenties and thirties of a succession of papers reporting renal failure as an acute and often fatal complication of surgical operations on patients with liver disease. (Walters and Parham, 1922, Heyd, 1924, Cave, 1926, Stanton, 1930 and Schutz et al. 1932).

Aspecial association between the liver disease and the renal dysfunction was proposed, and it was suggested that the syndrome be described by such terms as "Liver Death," "Hepato-renal Syndrome," "Uro-hepatic Syndrome," etc.

The development of the renal failure was ascribed to the release of hepatic nephrotoxins. (Heyd, 1924, Helwig and Schutz, 1932) or failure of a damaged liver to neutralise toxins produced elsewhere in the body (Heyd, 1924). With increasing understanding of the systemic manifestations of acute circulatory failure, acute hepatic failure and septicaemia, increasing doubt was expressed as to the validity of ascribing the onset of renal failure in these patients to a single factor. Thus Heyd (1924) and most of the early proponents of the hepato-renal syndrome had failed to distinguish between primary renal failure and renal failure complicating shock. Further, death was attributed to renal failure in many patients in whom, from a study of the published data, death due to acute liver failure or septicaemia had not been satisfactorily excluded. Colp and Ginzborg (1937) in a careful study of ten patients with obstructive jaundice, who died of renal failure following surgery, commented on the persistent hypotension noted post-operatively in 3 of these cases and suggested that the most important factor in the aetiology of their renal failure was a reduced cardiac output and pre-renal circulatory failure. Moon (in the discussion following a paper presented by Heyd in 1943) pointed out that many of the features of the hepato-renal syndrome, as described by Heyd, could be due to shock. The need to consider sepsis as a possible factor in the production of the hepato-renal syndrome was emphasised by Touroff (1936), who drew attention to a very high incidence of sub-clinical infection in patients following operation for the relief of jaundice. The following year Colp and Ginzborg reported that seven of their ten patients, who developed uraemia after operation, had evidence of infection (bronchopneumonia, pyelophlebitis, pancreatitis or cholangitis) at necropsy. One of these patients was reported as having bacterial nephritis, and it is of interest to note that some years before, Bartlett (1933) had suggested that chronic biliary tract infection was associated with a high incidence of bacterial nephritis.

The most serious objections to recognising a special syndrome of renal failure due to liver toxins, stemmed from advances in knowledge of the mechanisms of acute uraemia in non-jaundiced patients subjected to operation, trauma, etc. Following the clinical descriptions and post-mortem studies of the "crush syndrome" by Bywaters and his co-workers, (Bywaters and Beall, 1941, Bywaters and Dibble, 1942) it was soon realised that acute renal failure, characterised histologically by tubular necrosis, was a complication which might arise in many conditions associated with hypotension and circulatory failure, with or without the release of nephrotoxins into the blood stream (Maegraith et al., 1945, Lucke, 1946, Moon, 1947, Oliver et al. 1951).

A review of the clinical histories and pathological reports on patients developing acute renal failure following surgical relief of jaundice, showed that it was probable that many of these cases had developed acute tubular necrosis. Since this syndrome has been recognised, all published reports of patients with acute renal failure complicating obstructive jaundice have emphasised the occurence of hypotension and dehydration, preceeding the onset of renal failure and in most cases histological studies of the kidney have shown the changes typical of ischaemic tubular necrosis. (Malm, 1952, Lassen and Thomsen, 1958, Cohen et al. 1957, Andreassen et al. 1961) Not all patients have been operated on; sixteen of the twenty cases reported by Lassen and Thomsen, had had no operation prior to the onset of renal failure, but all had hypotension associated with severe dehydration or salt depletion.

Seven patients with obstructive jaundice, complicated by acute renal failure were seeen personally during the period of the present study. Severe hypotension preceeded renal failure in four, and probably occurred in two more. In only one was there no evidence of a fall in blood pressure. Kidney tissue was obtained from six of the seven patients, and in all instances showed histological changes compatible with a diagnosis of acute tubular necrosis.

There can be no doubt, therefore, that acute renal failure developing in patients with obstructive jaundice is commonly due to ischaemic tubular necrosis.

The demonstration of acute tubular necrosis in the patients, does not, however, complete our understanding of the association of renal failure with obstructive jaundice.

Most important among the questions that remain unanswered is, whether or not acute renal failure develops more commonly in patients with jaundice, than in non-jaundiced patients, where there has been comparable dehydration, hypotension or surgical trauma. Williams et al. (1960) reported fatal uraemia as a complication of surgery for the relief of obstructive jaundice in six per cent of 350 cases. They do not, however, report the incidence of fatal uraemia in non-jaundiced patients undergoing comparable operations, nor has it been possible to obtain this information from other sources. A retrospective study of the case records at Saint Bartholomew's Hospital was undertaken, but proved unsatisfactory, because of incomplete documentation. No other published series can be found, which clearly reports the incidence of renal failure as a complication of obstructive jaundice.

Although it is not possible to compare the incidence of acute renal failure in obstructive jaundice with its occurance in other surgical conditions, further evidence suggesting an association between the two conditions can be obtained from a study of the patients referred to special centres for the treatment of acute renal failure.

Andreassen et al. (1961) reported that among 132 patients admitted to an haemodialysis unit with acute uraemia, 86 had developed this in association with trauma, surgical disease or operation. Of these 86 patients, 29 or 34% had biliary tract disease and 72% were jaundiced at the onset of renal failure. Since publication of this paper, a further 10 cases of anuria in patients with biliary tract disease have been seen by these authors, 8 of whom were jaundiced before developing renal failure (Andreassen and Thaysen, 1963).

Balsløv and Jørgensen (1963) report that, of 184 patients developing acute anuria in whom there was underlying surgical disease, 31% had been operated on for disease of the biliary tract (jaundice not specified). This was the largest single group in their series.

Lassen and Thomsen (1958) noted an incidence of anuria in association with obstructive jaundice in 7% of 300 consecutive patients with acute renal failure from all causes.

Conclusive proof of an unusually high incidence of acute renal failure in patients with obstructive jaundice is not available, but the evidence is highly suggestive. It is certainly widely believed that there is some special association between the two diseases in humans. (Malm, 1952, Williams et al. 1960, Andreassen et al. 1961 and Balsløv and Jørgensen, 1963) In support of these conclusions, based on clinical material, are the results of a series of animal experiments, carried out by Nestel (1955) and Fajers (1956).

Nestel performed two series of experiments on rats. In the first series the effect of tourniquet shock (the application of a tourniquet for $4\frac{1}{2}$ hours to one hind limb) on the kidneys, was studied in animals, with and without bile duct ligation. The experiment was well controlled and evidence of renal damage was assessed on the histological findings in the kidneys.

EXPERIMENT	BILE DUCT TIED	TOURNIQUET	RENAL LESIONS		
		SHOCK	NONE	SLIGHT	SEVERE
1a	-	15	13	2	-
1b	14 survived	-	13	1	-
	1 died (Peritonitis)	-	-	-	1
1c	12 survived	12	-	-	12
	3 died	3	-	3	-

Effect of bile duct ligation and/or tourniquet shock on rat kidneys. (45 rats)

As can be seen from the table, tourniquet shock produced much more severe renal damage in the jaundiced animal, than it did in the non-icteric rat. The table also shows that these changes could not be attributed to obstructive jaundice alone.

In the second series of experiments, the effect of parenchymal liver damage was studied in addition to the effects of shock and obstructive jaundice. Liver damage was induced by the injection of small amounts of carbon tetrachloride. (The dose of this substance, that would produce detectable liver damage without renal tubular necrosis, had been determined by previous experiments.)

EXPERIMENT	$C.Cl_4$	BILE DUCT TIED	TOURNIQUET SHOCK	RENAL LESIONS NONE	SLIGHT	SEVERE
CONTROL	10	-	-	8	2	-
2a	8	8	-	1	6	1
2b	8	-	8	5	3	-
2c	12	12	12	1	-	11

Effect of carbon tetrachloride, with or without obstructive jaundice and/or tourniquet shock on rat kidneys. (38 rats)

The table shows that in the doses used, carbon tetrachloride alone produced minimal renal damage. The most severe damage was produced when all three procedures were carried out on the animals, but the extent of the damage was no different from that obtained in the first set of experiments with combined tourniquet shock and obstructive jaundice. Nestel rightly concludes that in the rat, the presence of liver necrosis does not affect the severity of the renal damage produced by the combination of tourniquet shock and obstructive jaundice.

In 1955, Fajers reported extensive studies on the histological and functional effects of temporary ligation of one renal artery in rabbits. A year later, when reporting further experiments, he states that obstructive jaundice predisposes the rabbit's kidney to damage, following temporary ischaemia. This degree of renal damage was not produced by either ten minutes renal ischaemia or obstructive jaundice alone.

Both these series of animal experiments lend support to the hypothesis that obstructive jaundice predisposes the kidneys to the development of acute renal failure in man.

The Nature of the Association

Acceptance of the belief that obstructive jaundice predisposes to the development of acute renal failure demands consideration of the possible mechanisms involved. Although acute tubular necrosis appears to be the most important factor in the pathogenesis of the renal failure, it cannot be concluded that the increased incidence of uraemia is solely dependant on this. The functional consequences of tubular necrosis may be mild or severe. Hayes (1957) reported serial renal function studies in 22 patients with 25% or more reduction in systolic blood pressure during operation. Nine of the 22 had reductions in urea clearances of 20-60% without elevations in the blood urea. All subsequently recovered normal function. He attributed the reduced clearances to acute renal damage incurred during the period of hypotension and concluded that "acute renal failure is not a fixed disease entity, but may be manifest in clinical experience, as a spectrum of alterations in renal function." Ladd (1955) also demonstrated subclinical renal damage in battle casualties in Korea.

Such mild degrees of renal damage, in patients with obstructive jaundice, may summate with pre-existing renal impairment to produce azotaemia. In considering the incidence of renal failure following operations in jaundiced patients, it is thus essential that the effect of the obstructive jaundice on renal function prior to operation be known.

While extensive studies on the pathological changes found in the kidneys of patients with obstructive jaundice have been described, the functional significance of these changes is poorly documented. In general no significant abnormality of the glomerular tuft is found and a specific glomerulitis has never been suggested in this condition, as has been claimed to occur in hepatic cirrhosis (Barr and Sommers, 1957, Bloodworth and Sommers, 1959 and Fisher and Hellstrom, 1959). This absence of glomerular changes has been used as evidence against significant abnormalities in glomerular filtration rates, although these have seldom been measured. The dominant lesions seen in the jaundiced kidney are in the proximal tubules and include bile pigmentation and varying degrees of hydropic vacuolation. Dilatation of the distal convoluted and collecting tubules, with flattening of the lining epithelial cells is seen and the lumina of the tubules contain pigmented casts. Apart from the bile pigmentation, the changes are in no way specific, similar changes being found as a result of the action of nephrotoxins of various kinds. (Oliver et al. 1951, Allen

1962) Despite these findings, scarcely any studies have investigated renal tubular function.

Abnormal tubular function could be related to the development of renal failure in at least three ways. Tubular damage may predispose to the back diffusion of waste products, as has been suggested by Meyer et al. (1941). This is believed by many to be of great importance in the development of uraemia in acute tubular necrosis. Tubular defects in the conservation of sodium or water in patients with jaundice would predispose to the development of hypovolaemia and hypotension in the presence of inadequate intake or excessive extra-renal losses. Finally, evidence of disturbed tubular function would lend support to the possibility that the histological changes seen indicate "sick cells," that is, cells that are more prone to damage by acute renal ischaemia.

The information available on renal function in obstructive jaundice has been reviewed and amplified by personal observations.

Glomerular Filtration Rate and Renal Blood Flow

Most experienced physicians agree that retention of nitrogenous waste products is not a feature of prolonged, uncomplicated obstructive jaundice. (Sherlock, 1958, Popper and Schaffner, 1957) Ayer (1940) reported his findings in 18 infants, who survived for 23-374 days with congenital atresia of the bile ducts. None had oliguria or uraemia although histological examination showed the changes typical of the kidney in jaundice. The absence of elevation in blood urea levels is not, however, synonymous with normal glomerular filtration rates. This was first pointed out by Wilensky (1927a and b.) in respect of pre-operative studies on a mixed group of patients, and has been emphasised in respect of jaundiced patients by others. (Bartlett, 1933, Schmidt and Chesky, 1948)

However, even mild renal damage might be expected to become manifest in a condition, such as obstructive jaundice, which may exist for many years, assuming that the renal damage is progressive. Some observers, (Farquhar, 1949 and Wilbur, 1934) commenting on the presence of proteinuria only in the early stage of jaundice, suggest that this is evidence of early and non-progressive damage.

Stewart and Cantarow, (1935) in the course of animal experiments on obstructive jaundice, postulate that renal tubular cells degenerate following the development of jaundice and are replaced by cells which are more resistant to the further action of the toxin. It is possible, therefore, that the situation in acute obstructive jaundice is not analagous to that in chronic jaundice.

Popper and Mandel (1937) performed creatinine clearances on five patients with obstructive jaundice and found moderately reduced values - 82-116 ml./min. compared with a normal of 96-162 ml./min. Popper (Meyer et al., 1941) states that this was confirmed in a further series of 16 patients. Elsom (1937) performed urea clearance studies on 16 patients, described as having obstructive jaundice, and reported that the values were less than 60% of normal in 7 out of the 16, although all had normal blood urea levels. The clearances were estimated on 12 hour collections of urine with one blood level, and the value of such estimations may be questioned. Further study of the paper also reveals that two of the patients had "catarrhal jaundice," one had cirrhosis and in one, the cause of jaundice was undetermined; the findings in this report must, therefore, be viewed with caution.

Schmidt and Chesky (1948) using the more conventional urea clearance test of Van Slyke (Moller et al. 1929) reported studies on 5 patients with obstructive jaundice. Although all had normal non-protein nitrogen levels in the blood, urea clearance was reduced to between 45 and 68% of normal in all. These patients developed renal failure post-operatively, and it has not been made clear whether they were selected for reporting on this basis, nor to what extent reduced urea clearances occur in patients with obstructive jaundice, who do not develop renal failure.

More recently, Cavazutti et al. (1952) using a thio-sulphate method to measure glomerular filtration rate, reported reductions to between 42 and 81 ml./min. in 14 of 17 patients with obstructive jaundice. They also reported increases in glomerular filtration rate following relief of the jaundice, continuing for periods up to 60 days after operation. Paris (1953) using a similar method, reported that two-thirds of 17 patients with obstructive jaundice had significant reductions in glomerular filtration rate. Giraud (1955) performed creatinine clearances on 6 cases, and in 3, found moderate reductions in the clearance values.

Nociti, (1958) in the only paper found reporting simultaneous measurement of glomerular filtration rate and renal plasma flow, studied 6 patients with calculus induced obstructive jaundice and 8 patients with obstruction due to carcinoma. All showed reductions in glomerular filtration rate and reduced clearances of P.A.H. The filtration fractions were increased in all. Studies performed after the relief of jaundice, showed a rapid return to normal values.

Thompson et al. (1940) used phenolsulphthalein (P.S.P.) excretion rates to measure renal function, and claimed that normal results were obtained in patients with obstructive jaundice. They also reported the results of pre-and post-operative P.S.P. excretion tests on 3 dogs subjected to bile duct ligation. Two showed slight decreases and one showed an increase in excretion. Their interpretation of these results is open to question; for it has been shown that obstructive jaundice per se alters the renal excretion rate of P.S.P. (Abrahamson, 1926, Hanner and Whipple, 1931 and Bartlett, 1933). Normally a proportion of the injected dye is excreted in the bile. In the presence of biliary obstruction, this does not occur and larger amounts are presented for renal excretion, and Hanner and Whipple (1931) produce good evidence indicating that renal P.S.P. excretion increases by 10-20%, immediately following bile duct ligation in dogs. It can be argued, therefore, that the findings of Thompson et al. indicate a reduction in the renal excretion of P.S.P.

It would, therefore, appear from these studies, that obstructive jaundice may lead to alterations in glomerular filtration rate, which some authors consider slight and others severe.

Our own studies on 21 patients with obstructive jaundice showed only small reductions in glomerular filtration rate and P.A.H. clearance, and in many patients the values obtained were within normal limits. Further, it is known that in the 2 cases with the lowest values, there was associated nephrosclerosis and it is possible that this was also present in other patients studied. Although the reduction in Inulin and P.A.H. clearance, and the elevation in Filtration Fraction in males reach the 1% level of significance, the mean values of 102 ml./min., 455 ml./min. and 0.23 respectively do not indicate impressive changes. Furthermore, it must be borne in mind that the recognised normal values for Inulin, P.A.H. and creatinine clearances are those obtained on healthy adults aged 15-45 years, while the mean age of the present series is 56 years and it is well established that the process of ageing is accompanied by reduction in renal clearances (Shock, 1946 and 1952). The results of this study certainly do not suggest that obstructive jaundice has seriously disturbed these aspects of renal function. It is worth noting that in the two patients who developed renal failure post-operatively, both had normal glomerular filtration rates and in the one patient in whom it was studied, renal plasma flow was not reduced. Whether the small reductions in Inulin and P.A.H. clearances found in the group as a whole can be attributed to the jaundice could not be investigated as studies following relief of jaundice, were available in too few cases.

In the animal studies, renal clearances were measured before, during and after jaundice. The results showed that in 17 dogs, there was a mean reduction of glomerular filtration rate of 20%. P.A.H. clearance fell by a mean value of 13%, and as no change in the renal extraction of P.A.H. was demonstrated in the presence of jaundice, this can be taken to represent a fall in effective renal plasma flow. Renal blood flow showed a similar mean fall. The filtration fraction, however, showed no significant change. Glomerular filtration rates and rates of renal plasma flow are notoriously unstable in anaesthetised dogs, being markedly affected by levels of anaesthesia, fluid or saline loading and anoxia. Special efforts were made in these studies to control these factors as carefully as possible.

Preliminary studies on normal and jaundiced dogs showed mean differences in Inulin clearance, measured on two occasions, as less than ± 10% in our hands. Clearances of P.A.H. varied by less than ±8% and renal blood flow by less than ±7%. We believe, therefore, that the reductions found in Inulin and P.A.H. clearance are meaningful, although small. A return to normal levels following the relief of jaundice in four dogs is evidence of a causal relationship between the jaundiced state and the reduction in the clearances.

These studies suggest that obstructive jaundice is associated with some reduction in glomerular filtration rates and renal blood flow. The reductions are not great and it is difficult to believe that the changes found could significantly contribute to the development of renal failure, unless accompanied by further severe renal damage.

This finding of reduced clearances is in agreement with the findings in previous published studies. The extent of the reduction is much less than that found by the continental workers. (Cavazutti et al. 1952, Paris, 1955 and Nociti, 1958) Comparison of the results demands consideration of the conditions under which the clearances were performed. Both glomerular filtration rate and renal plasma flow are, to a varying degree, affected by changes in blood pressure, dehydration, fever and analgesics. (Robinson, 1954) In our personal study, all patients were investigated, when normally hydrated, afebrile, and not receiving drugs, Information on these points is not provided in the above publications and the low glomerular filtration rates obtained, may be related to extra-renal factors.

All workers appear to agree that some reduction in glomerular filtration rate and renal plasma flow occurs in jaundice, but the reason for this fall has not been established. The most obvious suggestion is dehydration in ill patients, commonly prone to bouts of anorexia and vomiting. However, this was not the case in our patients and no correlation could be found, between blood volume changes and the fall in clearances in animals. Neither could the changes in glomerular filtration rate and renal plasma flow be related to change in weight or blood pressure in the dogs.

A significant correlation was, however, found in the animals, between the reductions in Inulin clearance and the degree of elevation of the serum bilirubin. Such an association was not found, with respect to P.A.H. clearance. No correlation was found in respect of the patients studied, by us or others. Nociti (1958) states that the fall in clearances, parallels the duration of the jaundice, but no figures are quoted. No such correlation is apparent in our material. It must be concluded that no satisfactory explanation can be given for the fall in clearance values at the present time.

Proteinuria in Obstructive Jaundice

The use of the term "cholaemic nephrosis" to describe the histological changes found in patients with obstructive jaundice has led to the mistaken belief by some, that proteinuria is a cardinal feature of the renal manifestations of jaundice. Although early reports claimed that it occurred to some degree in all patients, (Fitzhugh, 1929, Thompson et al., 1940) most studies showed that it is an inconstant feature. (Elsom, 1937, Ayer, 1940 and Wilbur, 1934). Wilbur (1934) believed that it was present mainly in the early stages of jaundice. None of these studies gave details of the 24 hour excretion of protein, but none suggested proteinuria of the degree found in the nephrotic syndrome. The term "cholaemic nephrosis," was in fact used to describe "a condition in which there are degenerative renal changes in contra-distinction to inflammation or nephritis." (Wilbur, 1934)

We found proteinuria in 20% of 25 patients, varying from 200-800 mg. per 24 hours. Electrophoresis of this protein showed a predominance of albumen, a finding typical of proteinuria secondary to glomerular damage. There was no suggestion of the "tubular protein" pattern which has been described in diseases characterised by tubular damage (Butler and Flynn, 1958 and 1961, Butler et al., 1962, Friberg, 1950 and Kazantsis et al., 1963). One dimensional paper or cellulose acetate electrophoresis of the urine in these conditions shows an unusually high proportion of protein, with a mobility similar to the $\alpha 2$ globulin fraction of serum, and often a relatively high proportion of $\beta 2$ globulin. It is of course possible that small amounts of tubular protein might have been demonstrated by the more refined two dimensional electrophoretic technique, described by Butler et al. (1962), but it seems unquestionable that the proteinuria of patients with obstructive jaundice is predominantly due to glomerular damage and not to tubular disease.

The occurrence of proteinuria could not be correlated with the degree or duration of jaundice, but in the one patient who was completely cured and who had no evidence of co-existing renal disease, the proteinuria disappeared after relief of jaundice.

Amino-aciduria and glycosuria

Both amino-aciduria and glycosuria are well recognised manifestations of acquired tubular disease (Mudge, 1958, Bickel, 1962). Reabsorption of these substances takes place in the proximal tubule, which is also the site of maximal histological change in obstructive jaundice. However, all 13 patients, on whom urinary amino-acid chromatograms were performed, showed normal patterns. No previous study can be found of urinary amino-acid excretion in obstructive jaundice but Sherlock (1958) states that amino-aciduria is not a feature of this condition. These findings are incompatible with the suggestion by Allen (1962) that the histological changes found in the kidney may be a consequence of amino-aciduria.

Glycosuria was found in three patients, but in all instances, was associated with a diabetic type of glucose tolerance curve and accompanied pancreatic disease. Renal glycosuria has not been reported in association with obstructive jaundice. The maximum tubular reabsorptive capacity for glucose was not measured, but there is no evidence for a defect in tubular reabsorption of glucose at normal blood levels.

Phosphaturia, the third classical manifestation of renal tubular disease, was not investigated, its significance in the absence of the other two being difficult to evaluate in obstructive jaundice, a condition which may be associated with defective absorption of Vitamin D.

The Renal Conservation of Water

An inability on the part of the kidney in obstructive jaundice to produce a concentrated urine, would not only confirm functional tubular damage in this condition, but also be of considerable importance as a factor predisposing to renal failure. Patients with obstructive jaundice commonly give a history of vomiting, and may in addition suffer considerable extra-renal losses of fluid in the post-operative period, due to biliary drainage and gastric suction. (Moore, 1959)

Failure of the kidneys to conserve water in these circumstances will increase the risk of dehydration, hypovolaemia, prerenal circulatory insufficiency and possibly tubular necrosis.

Clinical experience of obstructive jaundice does not suggest defective conservation of water; a lesion most commonly a feature of advanced glomerular failure. Acquired defects in concentrating ability are, however, well recognised in association with hypokalaemic nephropathy, in which tubular changes very similar to those found in cholaemic nephrosis are described.

Few studies have been reported on urine concentrating ability in patients with obstructive jaundice. Thompson et al., (1940) studying 32 patients with obstructive jaundice report urine specific gravities of less than 1015 in 6 patients and 1020 or less in 16. It is not clear, however, whether these estimations were made on urine samples obtained at random or after fluid deprivation. Lichtman and Sohval (1937) state that the urine specific gravity is usually normal in these patients even in the presence of oliguria and azotaemia, quoting Meczner's (1934) finding of normal specific gravities in 19 patients, but giving no further details. Others (Bartlett, 1933) describe cases with urines of low specific gravity, but careful study of the case histories suggests that renal failure, possibly due to tubular necrosis, was already established. Malm, (1952) however, described patients with pre-renal circulatory failure and uraemia in obstructive jaundice with urine of high specific gravity.

Our own studies of urine concentrating ability following pitressin tannate in oil, showed no significant defect in renal concentrating ability in any of the 21 patients studied. The use of this test, instead of the more stringent and less pleasant fluid deprivation test has been shown to be as satisfactory as the latter in detecting clinically significant defects in urine concentrating ability (de Wardener, 1956).

It seems well established, therefore, that obstructive jaundice is not accompanied by a significant defect in the renal conservation of water.

Acidification of the Urine

It has been proposed that metabolic acidosis, developing during surgery, and particularly in association with the use of an extra-corporeal circulation, may pre-dispose to renal shutdown. (Doberneck et al. 1962, Connolly et al., 1963) The part which may be played by pre-existing renal acidosis in this situation has hot been adequately studied.

Renal tubular acidosis has never been described in obstructive jaundice, nor was there any biochemical evidence of this in the 21 patients studied. Nevertheless, investigations of the kidney's capacity to acidify the urine, were included in our study as a further test of renal tubular function. Our results indicate a minor defect in acidification of the urine. The defect is slight and reversible, following the relief of jaundice. Neither blood pH nor total plasma CO_2 was measured during the tests, and it may be objected that comparable levels of acidosis were not obtained with and without jaundice. However, this seems unlikely as total hydrogen ion excretion was similar in those with and without jaundice. These changes are very like those described by Wrong and Davies (1959) in patients with the incomplete form of renal tubular acidosis.

The evidence is thus suggestive that obstructive jaundice leads to a mild defect in acidification of the urine by the renal tubule. The mechanism of this defect is unknown.

Sodium Conservation

Salt losing nephritis, first described by Thorn et al. (1944), is extremely rare, and in its fully developed form, has only been described in cases with advanced uraemia (Milne, 1963). The condition is characterised by excessive urinary excretion of large amounts of sodium, which is unaffected by mineralo-corticoids. Minor degrees of tubular resistance to aldosterone occur more commonly, but again, usually in association with chronic renal failure or transiently, following the relief of urinary tract obstruction. Defective sodium conservation is also a feature of the recovery phase of acute tubular necrosis. Renal salt wasting has not been described as a primary tubular defect in the presence of normal glomerular function.

In the only paper found, in which the renal handling of sodium in obstructive jaundice was studied, Giraud et al. (1955) claimed that there was a defect in sodium conservation in this condition. The circumstances under which sodium excretion was studied are not made clear and the evidence for defective reabsorption is based on measurement of the percentage of filtered sodium excreted. This can not be accepted as evidence of a renal defect in sodium reabsorption and indeed from the information furnished by the authors it is difficult to evaluate the significance of their observations.

It is stated by de Wardener (1962) that normal subjects, on a standard diet, when given 0.2 mg. of 9-α-fluorohydrocortisone twice daily, will reduce their excretion of sodium to less than 10 m.eq. per 24 hours. Using commercially available fluorohydrocortisone, we have been unable to confirm this. Higher doses are required to achieve maximal conservation and few normal controls have reduced their urinary sodium excretion to 10 m.eq. per day. For the purpose of studying sodium conservation in jaundiced patients, we gave 4 mg. daily of 9-α-fluoro-hydrocortisone to 9 patients on a standard ward diet and measured the daily excretion of sodium over 3 days, while on this dose. It would have been preferable to continue the study until a minimum steady state of sodium excretion was achieved, but this was not possible, because of the limited time allowed for these studies.

The response observed in the 9 jaundiced patients, was compared with that found in 7 non-jaundiced controls. No significant difference was found between the 2 groups. It is thus concluded that a renal defect in the conservation of sodium, which might pre-dispose to hypovolaemia, hypotension and renal circulatory impairment does not occur in patients with obstructive jaundice.

Renal Response to Haemorrhage

The small alterations we have found in renal function and blood flow in patients and animals with uncomplicated obstructive jaundice are insufficient to account for renal failure, either on their own or in the presence of moderate pre-renal circulatory impairment. This is consistent with the hypothesis that acute uraemia in these patients is a consequence of acute tubular necrosis following a period of acute renal ischaemia.

It is pertinent now to consider whether obstructive jaundice alters the renal circulatory responses to acute haemorrhage or hypotension in a manner which predisposes to renal ischaemia.

The effect of haemorrhagic shock on the renal circulation and function in normal dogs has been extensively studied, (Corcoran and Page, 1943, Van Slyke et al., 1944, Philips et al. 1945, and Selkurt, 1946) as has the effect of controlled reduction of renal arterial pressures by aortic crossclamping. (Winton, 1959) Rather less information is available on the effect of moderate haemorrhage on renal blood flow in the whole animal. Most studies of the effect of moderate blood loss, using clearance techniques, suggest that this results in only small reductions in renal blood flow, until the mean systemic pressure falls below 70-80 mm.Hg. (Philips et al., 1945, Smither, 1951). Hinshaw et al. (1961), using direct measurements, found that falls in renal blood flow closely parallel reductions in the blood volume and systemic pressure of all degrees. They also demonstrated that the fall in blood flow to the kidneys was proportionately much less than the reduction in blood flow to the limbs, thus confirming by direct measurements, the widely held belief that the renal circulation is preferentially safeguarded in the presence of hypovolaemia and hypotension. (Van Slyke et al., 1944, Smith, 1951) This reflects selective peripheral vaso-constriction without change, or with slight falls in renal vascular resistance.

It was considered possible that this pattern of response to haemorrhage might be disturbed by the jaundiced state, in such a way as to lead to renal circulartory impairment under conditions of acute hypovolaemia.

Two aspects of this problem were investigated. Firstly, the effect of the acute removal of 15 and 30% of the total blood volume, on glomerular filtration rate and P.A.H. clearance was studied in dogs before and after the production of obstructive jaundice. Secondly hypotension of between 60 and 70 mm. Hg. mean systolic pressure was produced by haemorrhage and maintained for 90 minutes. Blood was then replaced and glomerular filtration rates and P.A.H. clearance were measured 30, 60 and 90 minutes after complete blood volume correction.

An important consideration in the planning of these experiments was the method used to measure renal blood flow. Direct measurement of this by a reliable method is the procedure of choice, but the equipment required was not available. Previous workers have shown that the use of indirect measurements of renal blood flow, such as Diodrast (Corcoran and Page, 1943) or P.A.H. clearances (Phillips et al., 1945, Selkurt, 1946) are reliable, providing the following limitations are recognised. The clearance of these substances is a measure of effective renal plasma flow, only so long as their extraction by the kidney is known and is constant. Phillips et al. (1945) and Selkurt (1946) showed that extraction remains normal and constant until the mean systemic pressure is reduced below 80 or more usually 60 mm.Hg. - a pressure at which renal blood flow, measured by other means is reduced to 3% of normal. Secondly, in the recovery phase, following severe hypotension of this order, spurious results may be obtained for the renal extraction and clearance of P.A.H. during the first 10-20 minutes. This has been attributed to the accumulation of P.A.H. within the renal tubular cells during the ischaemic phase and its subsequent washout with restroation of normal circulation.

On the basis of these previous studies, it was considered that the use of P.AH. clearances to measure renal blood flow was justified, provided that clearances were not performed on dogs with blood pressures below 80 mm.Hg. and that at least 30 minutes were allowed to elapse after blood replacement, when severe hypotension had been produced.

Following haemorrhage, urine flow rates diminish and despite careful bladder washouts and allowance for increased delay between urine formation and arrival in the bladder, successive clearance values showed greater variation than those obtained in the normal animal. This increases the difficulty in obtaining reproducible results and where successive values varied by more than 10% the results were discarded.

Intravenous infusion of physiological saline, given at rates of 0.7 ml./kg./min. has been shown to affect the response of the renal circulation to controlled hypotension (Shumacker, 1960) and for this reason, the infusions carrying Inulin and P.A.H. were reduced to a minimum and special care taken to give identical amounts of fluid to the same dog when jaundiced, as had been given during studies before jaundice. In general these infusions were given at a rate of less than 0.26 ml./kg./min. We believe that the volume of fluid given was insufficient to affect blood volume significantly. Further, as the same procedure was carried out on each dog before and during jaundice, these small infusions should not mask differences due to the jaundiced state.

Haemorrhage of 15 and 30% of the blood volume in 8 normal dogs resulted in a mean reduction in glomerular filtration rate of -5 and -9% respectively. P.A.H. clearance fell by -7 and -12%. These changes are of the same order as those found by Phillips et al. (1945). In the presence of jaundice, slightly greater falls were observed, but the difference was not statistically significant.

There was considerable variation in the results obtained on individual dogs and we believe that small differences in the renal circulatory response to haemorrhage cannot be detected in experiments of the type used.

However, it is also clear that haemorrhage of 15-30% of the total blood volume does not produce marked renal ischaemia in jaundiced dogs. This is probably related to the absence of significant changes in blood pressure with this degree of haemorrhage.

Seven dogs were subjected to hypotension for 90 minutes; clearance studies were not performed during the period of hypotension, as renal vasoconstriction and reduced renal blood flow has been repeatedly demonstrated in dogs with comparable degrees of shock. (Phillips et al., 1946, Selkurt, 1946) Similar degrees of vasoconstriction have also been demonstrated in man in oligaemic shock. (Lauson et al. 1944, Ladd, 1955)

Satisfactory resucitation of patients and animals as gauged by the systemic blood pressure level and peripheral circulation is usually accompanied by a return of renal blood flow to near normal limits. In some instances, however, renal vasoconstriction may persist, both in man (Ladd, 1955) and in dogs. (Kramer, 1962) In considering possible explanations for an increased incidence of tubular necrosis in obstructive jaundice the possibility that this might be associated with prolonged or excessive renal vasoconstriction following a period of hypotension was suggested. The animal studies showed, however, that blood replacement following 90 minutes hypotension, was accompanied by a rapid return of Inulin and P.A.H. clearances to pre-hypotension levels in both normal and jaundiced dogs.

Blood Pressure Changes in Obstructive Jaundice

Hypotension is an integral part of the clinical situation preceding ischaemic tubular necrosis. It is, therefore, essential that various aspects of blood pressure control in obstructive jaundice be considered. Reductions in blood pressure are not a feature of uncomplicated obstructive jaundice in contradistinction to the situation found inacuteor chronic parenchymal liver damage. (Sherlock, 1958) None of our patients, when adequately hydrated, showed any pre-operative hypotension and no significant reduction in mean systolic pressure followed the production of jaundice in dogs.

However, Zollinger and Williams (1956) claim that shock, due to acute or chronic blood deficit accounts for more than 50% of the post-operative deaths in patients with obstructive jaundice and Williams et al. (1960) produce experimental evidence showing that acute haemorrhage produces hypotension more readily in jaundice, than in non-jaundiced dogs.

In the course of our studies on renal blood flow following haemorrhage, measurements were made of mean systolic pressure. In dogs subjected to acute withdrawal of 15 and 30% of their blood volume, small falls in mean pressure were observed. Slightly greater falls were seen in the same dog while jaundiced, but the difference was not statistically significant.

When hypotension of between 60 and 70 mm. Hg. was being produced, it was observed that a smaller percentage of the total blood volume had to be removed to effect this in jaundiced, compared with non-jaundiced dogs. This difference was probably significant, but certainly not as marked as the difference found by Williams et al. (1960), as these investigators found that to produce comparable hypotension, 71% of the blood volume had to be removed from normal dogs, but only 37% from jaundiced dogs. Our figures were 50% and 40% respectively.

These results suggest that jaundiced dogs may be more prone to develop hypotension in the presence of haemorrhage. Considerable blood volume deficits are involved, of a size not likely to occur in patients developing ischaemic tubular necrosis. The significance of these animal experiments in regard to the situation in man, must, therefore, be questioned.

Comparable studies cannot be performed on humans, but we have observed an interesting and relevant phenomenon inpatients undergoing haemodialysis. The use of the Kolff Twin Coil artificial kidney is inevitably associated with loss of fluid by the patient due to ultrafiltration by the coil and patients undergoing haemodialysis who are initially normally hydrated, require fluid replacement. We have observed, that patients with obstructive jaundice appear to be more sensitive to fluid loss than other anuric subjects, failure to make good their deficit being rapidly followed by hypotension. This is readily controlled by small infusions of whole blood.

It, therefore, appears that patients with obstructive jaundice are prone to hypotension, and the possible mechanisms involved must be considered.

The most enthusiastic supporters of this concept are Zollinger and his co-workers in Columbus, Ohio. They first produced evidence (Ellison et al., 1953) to suggest that patients with obstructive jaundice had reduced blood volumes. Subsequently they claimed that the observed high incidence of operative and post-operative shock in patients with obstructive jaundice was due to pre-operative blood volume deficits. In support of this Williams et al. (1960) pointed out that the increased tendancy of jaundiced dogs to develop hypotension following haemorrhage was associated with reduction in blood volume. These workers envisage a state of compensated oligaemia, in which these patients, despite blood volume deficits, maintained normal blood pressures by compensatory vaso-constriction. If further hypovolaemia occurrs, or vaso-dilatation due to anaesthesia, these compensatory mechanisms fail and acute hypotension develops.

However, before this explanation for the hypotension in jaundice can be accepted, it is essential to consider the evidence for blood volume deficits. Blood volume is readily measured, but the results obtained may be interpreted in different ways. It is usual to express the blood volume in relation to body weight or surface area, measured at the same time. This raises no problem in healthy subjects, but in ill patients, many workers, including Ellison et al. (1955), have chosen to express the result in relation to the weight of the patient prior to their illness, and not the weight at the time of carrying out the measurement. This practice has been criticised by Peden et al. (1960) and Blakeley et al. (1962) who claim that the weight at the time of the study should be employed. The implication of the first method is that loss of weight and tissue is not accompanied by a reduction in the capillary bed supplying the tissue.

While not denying that the absolute volume of blood diminishes in wasted patients, Peden et al. and Blakeley and his co-workers claim that this is accompanied by a proportionate reduction in the vascular bed. In support of this contention, they cite the studies of Keys et al. who showed that starvation of otherwise healthy men was accompanied by reductions in total blood volume, but this maintained the same relationship to body weight. Further they quote observations of their own and others in respect of blood transfusions given to debilitated subjects. Peden et al. (1960) transfused a group of patients calculated to have blood volume deficits, on the basis of their normal weights. In every instance the blood volume rapidly returned to the pre-transfusion level, plasma volume being reduced by an amount equal to the volume of transfused red cells. Similarly Williams and Parsons (1958) studied 100 patients with various diseases, whom they believed had blood volume deficits on the basis of their normal weight. The deficit was corrected by blood transfusion, but blood volumes returned to pre-transfusion levels, within 1 to 7 days.

These studies give good reason for believing that it is correct to express measured blood volume on the basis of actual, rather than expected body weight.

Ellison et al. (1955) give insufficient data to allow re-calculation of their results in this way, but it is interesting to note that the reduction in blood volume found in jaundiced dogs by Williams et al. (1960) accompanied weight loss.

Blood volume studies were carried out by us on 14 patients and all the dogs. The blood volumes, observed in patients, when expressed in respect of their weight, were within the normally accepted limits. (Blakeley et al. 1962) In the case of the dogs, although the actual volume of blood in any one dog diminished following the production of jaundice, when calculated ona body weight basis, small increases were apparent. Further, we could not correlate the increased pre-disposition to severe hypotension following haemorrhage in the jaundiced dogs with the absolute change in blood volume.

On the basis of these studies, we submit that the blood volume in jaundiced patients, is appropriate to the vascular compartment, and that blood volume changes are not the cause of an increased tendancy to hypotension. A practical corollary to this is that patients with obstructive jaundice do not require pre-operative blood transfusion to make good theoretical deficits as was suggested by Zollinger and Williams (1956). Indeed Peden et al. (1960) report fatal overloading of the circulation, when this has been done.

A further aspect of blood volume changes in obstructive jaundice, discussed by Williams et al. (1960) requires consideration. These workers suggested that, not only did jaundiced dogs have inadequate blood volumes, but also that this was associated with a reduced renal blood flow, although they produced no data to substantiate this statement. Our studies do not agree with either of these claims.

Other possible mechanisms, which might predispose to hypotension in patients with obstructive jaundice were not investigated in the present study, but certain possibilities may be briefly discussed.

The mean pressure within the arterial system is determined, not only by the blood volume, but also by the cardiac output and the total peripheral resistance (Rushmer et al. 1962). The development of acute hypovolaemia normally elicits complex cardio-dynamic and neuro-humoral responses. It is possible that obstructive jaundice may affect all or any of the mechanisms involved.

Peripheral vasodilatation is a feature of parenchymal liver failure, but is unusual in obstructive jaundice with sub-clinical liver damage. (Shorr et al., 1948, Shorr et al., 1951, Sherlock, 1958) Bile acids, however, possess anticholinesterase activity (Popper and Schaffner, 1957) which not only account for the bradycardia in obstructive jaundice, but may depress neuro-muscular and cerebro-spinal reflexes. (Sobotka, 1937) Bile retention is also said to lead to "toxic myocarditis." (Reich, 1954) To determine the extent to which any of these factors are of importance in patients with obstructive jaundice would require precise measurement of cardiac output and peripheral resistance following induced hypovolaemia in normal and jaundiced subjects. We are not aware of any such studies. Clinical assessment of peripheral blood flow in jaundiced dogs subjected to severe blood loss, did not suggest a serious defect in compensatory vaso-constriction. However, it is worth noting the observation of Williams et al. (1960) that hypotension may occur in patients with jaundice, without any increase in pulse rate. We can confirm this observation from our clinical experience, and suggest that it is evidence of abnormal cardio-dynamic responses in the presence of jaundice, related to the bradycardia found in this condition. A failure of the heart rate to increase in the face of hypovolaemia will contribute to hypotension. This feature of hypotension in jaundice is of considerable clinical importance, as no reliance can be placed on changes in pulse rate as an index of blood loss - blood pressure recording being essential.

An important mechanism in the pathogenesis of hypotension, which has received insufficient attention in jaundiced patients is the part played by infection. In the past decade, considerable attention has been paid to the association between bacterial infection and shock. (Waisbren, 1951, Weil and Spink, 1958 and Spink, 1960a.) Experimental and clinical studies show that while shock may be a consequence of infection with a variety of organisms (Smith, 1960), gram-negative bacilli are the most important group of pathogens involved. There is good evidence that coliform bacilli on disintegration release endotoxins, which produce acute hypotension, by a direct action on the vasculature. (Spink 1962) Infection with gram negative bacilli is a common complication of biliary tract disease (Lester, 1947) and interference with the hepatic blood supply, consequent on surgical trauma, during biliary tract surgery, predisposes to sepsis. (Markowitz et al., 1949, Tanturi et al., 1950 and Aitd, 1957) Intrahepatic or extrahepatic infection was believed to account for 9 out of 39 deaths following surgery on the biliary tract, reported in a recent study. (Glenn and McSherry, 1963) A review of the early reports on patients dying "liver deaths" after surgery, suggests that in most instances, death was due to irreversible shock and careful post-mortem studies of similar patients show a high incidence of concealed sepsis (Touroff, 1936 and Colp and Ginsborg, 1937). Many of the reports in the French literature have emphasised the importance of sepsis in the pathogenesis of renal failure in patients with obstructive jaundice. (Louyot et al., 1956, Plauchu et al., 1956 and Demeulenaere et al., 1957)

A study of the patients, operated on for jaundice in this hospital over the past 3 years, showed that infection preceded or followed surgery in 5 out of the 7 patients, in whom operation was complicated by hypotension and renal failure. In addition to the part infection may play in producing shock, there is some experimental evidence (Hinshaw and Bradley, 1957) that bacterial endotoxin can produce vaso-constriction by a direct action on the renal vessels.

Staphylococcal exotoxin certainly produces intense renal vasoconstriction in experimental animals. (Thal, 1955, Thal and Egner, 1961)

We believe that bacterial infection must be seriously considered as a possible factor in the production of shock and renal ischaemia in patients with obstructive jaundice.

Finally we must discuss other less well defined aspects of acute tubular necrosis, in respect of obstructive jaundice. It is agreed that renal ischaemia is the most important factor in producing this and is usually associated with systemic circulatory insufficiency and hypotension. However, the correlation of renal damage with the state of the systemic circulation is often poor. (Ladd, 1955, Merrill, 1962) This may be related to local renal vasoconstriction in the absence of hypotension; to the action of nephrotoxins acting alone or in conjunction with renal ischaemia or to variable sensitivity of the kidney cells to ischaemic anoxia. (Maegraith, 1945, Lucké, 1946, Oliver, 1951, Ladd, 1955 and Franklin and Merrill, 1960)

To consider the first of these possibilities, it has been shown that induction of anaesthesia and minor surgical procedures may produce abrupt depression of renal clearances in the absence of severe hypotension (Miles et al., 1952, Ladd, 1955). It is difficult to estimate how often this happens in general surgical practice and how often it leads to renal damage, particularly as Ladd (1955) and Hayes (1957) have shown that trauma and surgery may lead to sub-clinical renal damage detectable only by clearance studies. To assess whether surgery to the biliary tract, in the presence of jaundice, produced significant renal damage, whether or not hypotension occurred, we carried out endogenous creatinine clearances on 15 patients before and 7-9 days after operation. For comparison, similar studies were performed on 17 non-jaundiced patients undergoing cholecystectomy and on 5 patients having a partial gastrectomy. Changes in clearances were small and no difference was demonstrated between jaundiced and non-jaundiced patients. We concluded that uncomplicated abdominal surgery does not cause significant renal damage in either jaundiced or non-jaundiced patients.

The importance of nephrotoxins and altered sensitivity of the tubular cells to ischaemia in jaundice was not studied, but Fajer's (1956) experiments, which have already been discussed, indicate that the jaundiced kidney is more sensitive than normal to renal ischaemia. This suggests that in the jaundiced state, substances accumulate or are produced, which alter tubular cell function. This may or may not be the same factor or factors which produce the proteinuria and the slight alterations in renal function already discussed. Very little information is available about such nephrotoxins, but in conclusion, we will review the various factors, which have been considered to have nephrotoxic properties in obstructive jaundice. Many of the studies on which this information is based involved correlation of the degree of histological changes in the kidney with the blood level of the proposed nephrotoxin. The significance of the histological change in terms of renal function is poorly understood.

BILIRUBIN - The changes typical of cholaemic nephrosis are found in all forms of liver disease in which there is also hyperbilirubinaemia. (Lieber and Stewart, 1935, Ayer, 1940, Lucké, 1944 and Lucké and Mallory, 1946) The degree of pigmentation is related to the duration and intensity of the jaundice. (Stewart et al., 1935, Lucké and Mallory, 1946) Uys (1957) in rat experiments and Stewart et al. (1935) working on cats were unable to show any correlation between tubular cell degeneration and either the degree or duration of hyperbilirubinaemia. By contrast, in humans Lucké (1944 and 1946) compared the renal pathology in patients with subacute epidemic hepatitis, in whom jaundice was usually marked, with the changes found in fulminating hepatitis where jaundice was much less. He noted that tubular degeneration was much less common in the latter group. Elsom (1937) carried out Addis counts on the urine of 16 patients with obstructive jaundice and noted that the increase in casts found in the patients was proportional to the level of the serum bilirubin. They concluded that hyperbilirubinaemia did produce renal damage. However, changes in glomerular filtration rates and renal plasma flow have not been consistently related to serum bilirubin levels.

It would seem, therefore, that apart from leading to bile pigmentation of the kidney, the role of hyperbilirubinaemia in producing renal histological change or functional impairment in intact animals or humans is equivocal. Invitro studies on bilirubin cystotoxicity have demonstrated impairment of such cellular processes as respiration, (Day, 1954) oxidative phosphorylation (Zetterstrom and Ernster, 1956) and electron transport (Bowen and Waters, 1958). The role of bilirubin as a nephrotoxic agent cannot, therefore, be excluded, but requised further investigation.

BILE SALTS - The nephrotoxicity of bile salts is similarly ill defined, particularly as their accumulation usually accompanies bilirubinaemia. (Wooton et al. 1959) Nevertheless, it is widely supposed that bile acids are kidney toxins. This largely stems from the work of Stewart and Canterow (1935) who carried out a series of experiments on cats and dogs, into whom thqy injected controlled amounts of sodium dehydrocholate. This produced acute degenerative changes in the renal tubules and they concluded that the compound was nephrotoxic. This may well be true, but unfortunately this is not a naturally occurring compound. Horrall (1938) in his monograph states that the toxic effect of bile upon the kidneys can be produced by solutions of pure bile salts, but not by bile pigments. Regrettably, no other details are given. Lucké and Mallory (1946) claiming that bile salts may be nephrotoxic, state that in their studies of fulminant hepatitis, there was no renal tubular degeneration, because bile salt retention does not occur in this condition. However, no blood bile acid levels were given and it has since been shown (Wooton et al. 1959) that fulminant hepatitis may be accompanied by high bile acid levels in the blood.

We feel the nephrotoxicity of bile salts has not been conclusively demonstrated.

FLUID AND ELECTROLYTE DISTURBANCES - Kulka (1950) described vacuolar nephropathy in a variety of conditions associated with nutritional deficiency, fluid and electrolyte disturbances. The appearances described are very similar to those found in the kidneys in obstructive jaundice, apart from the bile pigmentation. More recent descriptions of the nephropathy accompanying potassium depletion (Relman and Schwartz, 1958 and 1962) also show similarities. Block et al. (1952) found that fluid and electrolyte deprivation increased the degree of tubular change in obstructive jaundice. The possible role of these factors in producing the renal changes typical of cholaemic nephrosis is difficult to assess; but we suspect that many patients with jaundice who have been shown to have reversible impairment of renal function may have had varying degrees of fluid and electrolyte depletion.

It is of interest to note that in our studies, although there was no evidence of hypokalaemia in any of the patients, they were shown to have a mild defect in urine acidification, which is also a feature of hypokalaemic nephropathy.

In conclusion, no single nephrotoxin can be positively identified in obstructive jaundice and indeed it is probable that any renal functional impairment or increased sensitivity to ischaemia in this condition, is the result of the interplay of several factors.

CONCLUSION

From these studies, we propose the following thesis regarding the association between obstructive jaundice and renal failure.

There is good evidence to indicate an especially high incidence of renal failure in patients with obstructive jaundice. This does not, however, occur in the absence of additional factors such as dehydration, haemorrhage or sepsis. Uncomplicated obstructive jaundice results only in slight abnormalities in renal function, insufficient on their own to cause uraemia.

Acute renal failure when it develops may be a consequence of dehydration and pre-renal circulatory failure, but is more commonly the result of acute tubular necrosis and experimental studies suggest that this is more readily produced by renal ischaemia in the presence of obstructive jaundice.

Renal ischaemia usually occurs in association with systemic hypotension and there is evidence that patients with obstructive jaundice are more liable to hypotension if hypovolaemia occurs. In addition, acute circulatory failure may result from the sepsis, which is a common complication of biliary tract disease.

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APPENDIX I

CASE ABSTRACTS

CASE 1. W. A., a 66 year old male clerk. Admitted with a four week history of persistent, painless jaundice, pale stools and dark urine. No vomiting or diarrhoea. No urinary symptoms. Weight loss of 6 lbs. in four weeks. No previous history of renal disease.

Examination: Obvious jaundice, but no stigmata of liver failure (liver palms, spider naevi, digital clubbing, wrist flap or foetor hepaticus). Blood pressure (B.P.) 190/120 mm. Hg.

Laboratory Investigations: Haemoglobin (Hb.) 13.9 G.%. White blood count (W.B.C.) 7,200 per cu. mm. Serum bilirubin 8.9 mg/100 ml. Serum proteins: Albumen 4.9 G.%; globulin 2.8 G.%. Serum alkaline phosphatase: 34.8 King-Armstrong (K.A.) units. Thymol turbidity: 1 unit. Serum glutamic-oxalic transaminase (S.G.O.T.) 43 units. Serum glutamic-pyruvic transaminase (S.G.P.T.) 26.5 units.

*

Urine examination: No protein; microscopy normal; culture sterile.

Operation: Two weeks after admission operation was preceded by the transfusion of two pints of whole blood. The operation

* The values for blood urea and serum electrolytes in this and all patients are given in Table 4.

was not difficult. The gall bladder was thickened and fibrosed, the site of chronic cholecystitis. The common duct was, however, patent, and operative cholangiography showed no evidence of extra hepatic obstruction of the bile passages. The bile duct was drained, a liver biopsy performed and the wound closed.

Recovery from the operation appeared normal for 48 hours. The patient then developed fever to 101°F and looked less well. No record of blood pressure was obtained at this stage. The daily urine output varied between 300 and 800 mls. After 24 hours the fever subsided spontaneously but the patient became increasingly ill with oliguria, hypotension and a rising blood urea. By the eighth post-operative day, when first seen by me the patient was comatose, hypotensive and acidotic. This blood urea was 306 mg./100 ml., serum sodium 114 m.eq/litre and serum potassium 7.5 m.eq/litre. Despite antibiotics, cation exchange resins and vaso-pressor agents, the patient died the following day.

Post-mortem examination confirmed the absence of extra-hepatic biliary obstruction, the histological appearances of the liver being compatible with primary intra-hepatic cholestasis. There was a perforation of the anterior aspect of the duodenum with unsuspected peritonitis. The lungs showed extensive bilateral bronchopneumonia. The kidneys were of normal size and showed little abnormality on macroscopic examination. Histological examination showed moderate numbers of small calculi scattered throughout the renal tubules. There were mild degenerative changes in the tubular epithelium, but no frank necrosis and little interstitial oedema or inflammation.

CASE 2. W. B., a 49 year old male shopkeeper. History of four weeks painless jaundice with pale stools and dark urine. Slight loss of appetite and weight loss. No previous history of renal disease.

Examination: Afebrile. Moderate jaundice. No stigmata of liver failure. Liver enlarged 5 cm. below the costal margin. B.P. 140/90 mm.Hg.

Laboratory Investigations: Hb. 14.1 G.%; W.B.C. 9,200 per cu. mm. Serum bilirubin 8.0 mg./100 ml. Serum proteins: albumen 4.3 G%; globulin 2.1 G.%. Thymol turbidity 1 unit. Zinc sulphate turbidity 2 units. Urine examination: protein present, but no excess of red blood cells or leucocytes. Cultures sterile.

Operation ten days after admission revealed a large carcinoma of the head of the pancreas with involvement of the regional lymph nodes. Cholecysto-jejunostomy and gastro-jejunostomy were performed. The patient recovered normally from the anaesthetic but died, suddenly, the following morning.

Post-mortem examination showed no satisfactory explanation for the death. The kidneys were of normal size and weight and showed no histological abnormality apart from bile staining and slight vacuolation of the proximal tubules.

CASE 3. H.B., a 40 year old male glass blower. One year's history of upper abdominal pain; three weeks' jaundice with pale stools and dark urine; anorexia with loss of 2 stone in weight in 18 months. No previous history of renal disease.

Examination: Afebrile. Pulse 60/min. - atrial fibrillation. B.P. 200/100 mm.Hg. Liver enlarged 6 cm. below the costal margin. No stigmata of liver failure.

Laboratory Investigations: Hb. 12.4 G.%. W.B.C. 6,300/cu. mm. Serum bilirubin 15.4 mg./100 ml. Serum proteins - albumen 4.3 G.%, globulin 2.76.%. Serum alkaline phosphatase 112 K-A units. Thymol turbidity 0.5 units. Zinc sulphate turbidity 2 units. S.G.O.T. 220 units. S.G.P.T. 95 units.

Urine examination: Normal. Culture sterile.

Laparotomy two weeks after admission revealed a large adenocarcinoma of the gall bladder, with extensive involvement of retro-peritoneal glands. No surgery was performed.

Post-operative progress: Rapid deterioration and death 18 days later. No oliguria or azotaemia. Permission for necropsy refused.

CASE 4. L.B., a 60 year old male draper. Six weeks malaise and abdominal discomfort. Three weeks jaundice with dark urine and pale stools. No previous history of renal disease.

Examination: Afebrile. No stigmata of liver failure. B.P. 140/90 mm.Hg. Large mass below the right costal margin.

Laboratory Investigations: Hb. 12.1 G.%. W.B.C. 5,200 per cu. mm. Serum bilirubin 10.8 mg./100 ml. Serum proteins: albumen 4.5 G.%, globulin 2.8 G.%. Serum alkaline phosphatase 48 K-A units. Thymol turbidity 1 unit. Zinc sulphate turbidity 3 units.

Urine examination: Normal. Culture sterile.

Operation ten days after admission showed a carcinoma of the head of the pancreas. A choledoco-jejunostomy was performed. Good initial recovery with diminution in the degree of jaundice. No oliguria or azotaemria. Serum bilirubin on discharge 1.8 mg./100 ml. Developed ascites and died in another hospital four months later. No post-mortem examination.

CASE 5. L.C., a 60 year old labourer. One month's abdominal pain; three weeks jaundice with pale stools and dark urine. Mild vomiting. Moderate weight loss. No previous history of renal disease.

Examination: Thin, ill and jaundiced. Afebrile. No stigmata of liver disease. B.P. 125/70 mm.Hg. Palpable mass right upper abdomen.

Laboratory Investigations: Hb. 12.4 G./100 ml. W.B.C. 7,600 per cu. mm. Serum bilirubin 9.2 mg/100 ml. Serum proteins: albumen 4.6 G.%, globulin 2.4 G%. Serum alkaline phosphatase 32 K-A units. Thymol turbidity 2 units. Blood Wasserman positive.

Urine examination: Protein present, no excess of cells. Culture sterile.

Laparotomy one week after admission showed a carcinoma of the head of the pancreas with lymph gland involvement and small liver metastases. Gastro-jejunostomy and cholecysto-jejunostomy were performed. Discharged after two weeks recovery, jaundice fading. Well for two months, then steady deterioration, mild jaundice and cachexia with death six months after surgery.

Post-mortem examination revealedan adenocarcinoma of the head of the pancreas, extensive carcinomatosis peritonei and liver metastases. Syphilitic aortitis and moderate coronary atheroma.

The kidneys were reduced in size. The capsules stripped with difficulty to reveal a finely granular surface. Microscopic examination showed extensive arteriosclerosis of the renal vessels with cortical scarring.

CASE 6. W.D., a 59 year old male clerk. Two year history of intermittent abdominal pain, one month's jaundice, anorexia and weight loss, pruritus and dark urine. No past history of renal disease.

Examination: Obese, afebrile and jaundiced. B.P. 170/110 mm.Hg. Liver enlarged 5 cm. below the costal margin. No stigmata of liver failure.

Laboratory Investigations: Hb. 16.0 G.%, W.B.C. 6,200 per cu. mm. Serum bilirubin 13.0 mg/100 ml. Serum proteins: Albumen 4.2 G.%, globulin 2.1 G.%. Serum alkaline phosphatase 25.5 K-A units. Thymol turbidity 1 unit. S.G.O.T. 64 units. S.G.P.T. 31 units.

Urine examination: Normal.

Operation two weeks after admission revealed an adeno-carcinoma of the ampulla of Vater. This was excised and the common bile duct anastomosed to the duodenum. There was a considerable amount of blood oozing and one pint of blood was given.

Initial progress was satisfactory but the second day he was obviously oliguric. This was associated with low grade fever (99°F) and progressive hypotension. The urine was of low specific gravity (1009) and contained protein. Treatment with intravenous tetracycline and vasopressor agents failed to control the fever or the hypotension. On the sixth post-operative day the blood urea was 245 mg./100 ml. and the serum potassium 5.2 m.eq./litre. The patient died suddenly on that day.

Post-mortem examination showed bilateral paracolic abscesses, but no evidence of bowel perforation. The choledocho-duodenostomy was patent and intact. The liver was of normal size and deeply pigmented, histological examination showed only mild centri-lobular necrosis. Both kidneys were enlarged, pale and bile-stained. On sectioning, the cortex bulged slightly and was clearly demarcated from the medulla. Microscopic examination showed bile pigmentation of the epithelium of the proximal tubules with extensive vacuolation of these cells. There was patchy degeneration of many nephrons, with a moderate infiltration of the interstitial tissue with inflammatory cells. Some of the tubules were dilated and contained bile-stained granular casts.

CASE 7. A.D., a 55 year old male baker. Six months intermittent right-sided abdominal pain, three weeks jaundice with pale stools and dark urine. Slight pruritus. Loss of one stone in weight in six weeks. Very occasional vomiting. No previous history of renal disease.

Examination: Afebrile, thin. No stigmata of liver failure. B.P. 110/70 mm.Hg. Liver enlarged 3 cm. below the costal margin.

Laboratory Investigations: Hb. 13.3 G./100 ml. W.B.C. 5,500 per cu. mm. Serum bilirubin 14.1 mg/100 ml. Serum proteins: albumen 5.2 G.%, globulin 1.7 G.%. Thymol turbidity less than 1 unit. Zinc sulphate turbidity 5 units. Serum alkaline phosphatase 29 K-A units.

Urine examination: Normal. Culture sterile.

Operation three weeks after admission showed an adeno-carcinoma of the pancreas. Cholecysto-jejunostomy was performed. Post-operative recovery was normal with fading of the jaundice. Post-operative radiotherapy was given to the abdomen and the patient was discharged after 3 weeks.

He deteriorated, with increasing abdominal pain and steatorrhoea. He was then given cyclo-phosphamide with no improvement. Five months after operation, he was admitted to a terminal care hospital and died a month later. No post-mortem was performed.

CASE 8. S.H., a 54 year old male hairdresser. One month's history of jaundice with loose, pale stools and dark urine. No pain. No previous history of renal disease.

Examination: Afebrile, moderate jaundice. No stigmata of liver failure. B.P. 120/80 mm. Hg. Liver enlarged 4 cm. below the costal margin. Gall bladder readily palpable.

Laboratory Investigations: Hb. 13.3 G./100 ml. W.B.C. 4,000 per cu. mm. Serum bilirubin 12.9 mg./100 ml. Serum proteins: albumen 4.2 G.%, globulin 2.0 G.%. Thymol turbidity 1 unit. Zinc sulphate turbidity 3.5 units. Serum alkaline phosphatase 130 K-A units.

Urine examination: Glycosuria present. Culture sterile.

Glucose tolerance test: Diabetic curve.

Operation ten days after admission showed a carcinoma of the head of the pancreas. A cholecysto-duodenostomy was performed. The immediate post-operative progress was normal. Two weeks after operation, he developed acute abdominal pain and evidence of peritonitis. Laparotomy showed that a pseudocyst had developed in relation to the pancreatic biopsy and this had then ruptured. Subsequent recovery was satisfactory with gradual relief of jaundice. At completion of this study, three weeks after operation, the patient was still slightly jaundiced.

CASE 9. A.H., a 58 year old male telephonist. Admitted to hospital because of repeated bouts of biliary colic. Two previous hospital admissions in the preceding two months with similar symptoms without jaundice.

Examination: Obviously jaundiced, afebrile, but in severe pain. Not dehydrated. B.P. 140/100 mm.Hg. Tender over the fundus of the gall bladder.

Laboratory Investigations: Hb. 16.4 G./100 ml. W.B.C. 6,200 per cu. mm. Serum bilirubin 5.0 mg./100 ml. Serum proteins: Albumen 5.5 G.%, globulin 1.2 G.%. Serum alkaline phosphatase 38 K-A units. Thymol turbidity 0.5 units. Zinc sulphate turbidity 0.5 units.

Urine examination: Normal.

Operation was performed one week after admission, because of persistant jaundice. At operation the common bile duct was slightly dilated, but no calculi could be found. Cholecystectomy was performed. The post-operative course was uneventful and jaundice subsided rapidly.

CASE 10. D.K., a 57-year-old male manufacturers' agent. Three weeks history of right-sided abdominal pain. Anorexia and loss of 1 stone in weight over three weeks. Two weeks jaundice with pale stools and dark urine. No previous history of renal disease.

Examination: Moderate jaundice. No stigmata of liver failure. B.P. 140/80 mm.Hg. Murphy's sign present.

Laboratory Investigations: Hb. 14.8 G./100 ml. W.B.C. 5,600/ cu. mm. Serum bilirubin 5.0 mg./100 ml. Serum proteins: Albumen 6.0 G.%, globulin 1.8 G.%. Thymol turbidity 0.5 units. Zinc sulphate turbidity 2 units. Serum alkaline phosphatase 37 K-A units. Urine examination: Protein present, but no excess of cells. Culture sterile.

Operation: Operation two weeks after admission revealed numerous biliary calculi including a stone impacted at the lower end of the common bile duct. The stones were removed and cholecystectomy and sphincterotomy performed. Post-operative recovery was uneventful.

CASE 11. G.K., a 58 year old male sales manager. Three weeks history of upper abdominal pain and increasing jaundice, stools pale and urine dark. Increasing anorexia, moderate pruritus. No previous history of renal disease.

Examination: Afebrile, moderate jaundice, no stigmata of liver failure. B.P. 130/90 mm.Hg. Liver enlarged 6 cm. below the costal margin.

Laboratory investigations: Hb. 13.9 G.%. W.B.C. 10,000 per cu. mm. Serum bilirubin 6.7 mg./100 ml. Serum proteins: albumen 4.5 G.%, globulin 2.4 G.%. Thymol turbidity less than 1 unit. Zinc sulphate turbidity 3.1 units. Serum alkaline phosphatase 39 K-A units. S.G.O.T. 60 units. S.G.P.T. 80 units.

Urine examination: Normal. Culture sterile.

Operation ten days after admission revealed an adenocarcinoma of the head of the pancreas with lymph node involvement. A cholecysto-jejunostomy was performed. Post-operative recovery was complicated by rupture of the abdominal wall requiring resuture. Jaundice diminished. Discharged ten days post-operatively. Serum bilirubin 1.5 mg./100 ml. Seen again three months later, when he had developed ascites. Died at home two weeks after this - no necropsy.

<u>CASE 12.</u> <u>J.L., a 62 year old male labourer.</u> Four weeks history of painless jaundice with pale stools and dark urine. Moderate anorexia and loss of weight over two to three months. No previous history of renal disease.

<u>Examination</u>: Afebrile. Jaundiced. No stigmata of liver failure. Irregular mass under the right costal margin. B.P. 160/110 mm.Hg.

<u>Laboratory Investigations</u>: Hb. 12.8 G./100 ml. W.B.C. 5,800 per cu. mm. Serum bilirubin 7.6 mg./100 ml. Serum proteins: albumen 4.1 G.%, globulin 2 G.%. Thymol turbidity 2 units. Zinc sulphate turbidity 4 units. Serum alkaline phosphatase 52 K-A units.

Urine examination: Normal. Culture sterile.

<u>Operation</u> three weeks after admission showed an extensive carcinoma involving the gall bladder, bile passages and glands in the porta hepatis. Surgery was impossible. Initial recovery was satisfactory but he deteriorated rapidly and died three weeks after operation. No oliguria or nitrogen retention. Permission for post-mortem was refused.

CASE 13. C.R., a 62 year old male catering officer. Intermittent diarrhoea for two months, painless jaundice for one month with pale stools and dark urine. Loss of 1 stone in weight in 6 weeks. No previous history of renal disease.

Examination: Afebrile, deep jaundice. No stigmata of liver failure. B.P. 130/80 mm.Hg. Liver enlarged 7 cm. below the costal margin. No other masses in the abdomen.

Laboratory Investigations: Hb. 12.7 G.%. W.B.C. 3,400 per cu. mm. Serum bilirubin 16.8 mg./100 ml. Serum proteins: Albumen 5 G.%, globulin 2.6 G.%. Thymol turbidity 2 units. Zinc sulphate turbidity 5 units. Serum alkaline phosphatase 27 K-A units.

Urine examination: Normal. Culture sterile.

Operation two weeks after admission showed a carcinoma of the head of the pancreas. Choledocho-duodenostomy and cholecystogastrectomy were performed. He recovered from the operation, but developed ascites before discharge. Serum bilirubin on discharge - 8.4 mg./100 ml. Over the subsequent nine months his jaundice improved considerably. He had intermittent ascites and developed glycosuria. Died nine months later. No necropsy.

CASE 14. J.R., a 49 year old male cotton wholesaler. Admitted with an acute cholangitis and jaundice of ten days duration. History of recurrent attacks of cholangitis and jaundice over the previous two years. Previous history of renal calculi with recurrent urinary infections for which right partial nephrectomy had been performed six years previously.

Examination: Febrile, jaundiced and in pain. Marked tenderness over the fundus of the gall bladder. B.P. 165/95 mm.Hg.

Laboratory Investigations: Hb. 12.7 G./100 ml. W.B.C. 6,000 per cu. mm. Serum bilirubin 4.2 mg/100 ml. Serum proteins: albumen 4.3 G.%, globulin 2.3 G.%. Thymol turbidity 1 unit. Zinc sulphate turbidity 5 units. S.G.O.T. 27 units. S.G.P.T. 55 units. Serum alkaline phosphatase 22 K-A units.

Urine examination: Protein ++. Microscopy - moderate numbers of red and white blood cells. Culture sterile.

The patient was initially treated with antibiotics and the fever subsided. Jaundice, however, deepened (serum bilirubin 12.8 mg./100 ml.).

Operation was performed nine days after admission. The common bile duct was obstructed by thick inspissated biliary mud. Cholecystectomy was performed and the bile ducts cleared. Culture of the bile grew coliform bacilli. The post-operative course was uneventful save for the development of a small stitch abscess. Jaundice gradually disappeared and the serum bilirubin on discharge was 0.9 mg./100 ml.

CASE 15. E.S., a 60 year old male market gardener. Two months history of upper abdominal discomfort and five weeks jaundice with pale stools and dark urine. Occasional vomiting for one week. Anorexia and weight loss. No previous history of renal disease.

Examination: Jaundiced. No stigmata of liver failure. Liver enlarged and tender. B.P. 175/105 mm. Hg.

Laboratory Investigations: Hb. 11.8 G./100 ml. W.B.C. 10,300 per cu. mm. Serum bilirubin 25 mg./100 ml. Serum proteins: albumen 4.5 G.%, globulin 2.1 G.%. Thymol turbidity 1 unit. Zinc sulphate turbidity 2 units. Serum alkaline phosphatase 39 K-A units.

Urine examination: Proteinuria, no excess of cells. Culture sterile.

Operation nine days after admission showed an adenocarcinoma of the head of the pancreas with multiple peritoneal deposits. Choledocho-jejunostomy was performed. Post-operatively the jaundice faded, but there was increasing ascites. Serum bilirubin at discharge was 4.2 mg./100 ml. The patient's general condition deteriorated fairly rapidly and he died three months after operation at another hospital. No necropsy was performed.

CASE 16. F.T., a 57 year old male teacher. Two months history of painless jaundice with pale stools and dark urine; anorexia and loss in weight. Left nephrolithotomy for renal calculi three years previously.

Examination: No stigmata of liver failure. Marked hepatomegaly. B.P. 160/100 mm.Hg.

Laboratory Investigations: Hb. 12.7 G./100 ml. W.B.C. 8,200 per cu. mm. Serum bilirubin 7.4 mg./100 ml. Serum proteins: albumen 4.7 G.%, globulin 2.3 G.%. Thymol turbidity 1 unit. Zinc sulphate turbidity 6 units. Serum alkaline phosphatase 30 K-A units. Urine examination: Normal. Culture sterile.

Operation ten days after admission showed many large stones obstructing the common bile duct. These were removed and cholecystectomy performed. Post-operative recovery was normal. The jaundice gradually faded but post-operative cholangiography suggested persisting obstruction at the lower end of the common duct. However, complete recovery has since been achieved with regression of hepatomegaly and complete loss of jaundice.

CASE 17. H.A., a 49 year old housewife. Three months intermittent upper abdominal pain with two weeks jaundice, pale stools and dark urine. No previous history of renal disease.

Examination: Afebrile, jaundiced; no stigmata of liver failure. B.P. 180/100 mm. Hg.

Laboratory Investigations: Hb. 13.6 G.%. W.B.C. 3,000 per cu. mm. Serum bilirubin 6.1 (on admission), later rising to 10.3 mg./100 ml. Serum proteins: albumen 6.0 G.%, globulin 1.4 G.%. Thymol turbidity 2 units. Zinc sulphate turbidity 4 units. Serum alkaline phosphatase 195 K-A units.

Urine examination: Normal. Culture sterile.

Operation three weeks after admission revealed a stone obstructing the common bile duct. The biliary passages were cleared and cholecystectomy performed. Post-operative course was normal with rapid disappearance of jaundice.

CASE 18. K.F., a 62 year old female clerk. Six weeks anorexia and malaise. Three weeks of painless jaundice with pale stools and dark urine. Moderate weight loss. Previous history of recurrent pyelonephritis.

Examination: Afebrile, deep, obvious jaundice and weight loss. No stigmata of liver failure. Liver markedly enlarged. B.P. 120/70 mm. Hg.

Laboratory Investigations: Hb. 11.8 G.%. W.B.C. 7,800 per cu. mm. Serum bilirubin 6.6 mg./100 ml. Thymol turbidity less than 1 unit. Zinc sulphate turbidity 9 units. Serum alkaline phosphatase 50 K-A units. Serum proteins: albumen 3.9 G.%, globulin 3.3 G.%. Electrophoresis showed an increase in β globulin. S.G.O.T. 34 units. S.G.P.T. 18 units.

Urine examination: Trace of protein. Culture sterile.

Operation two weeks after admission revealed a carcinoma of the ampulla of Vater. This was excised and a polythene tube inserted into the common bile duct and pancreatic duct and the duodenal wall was closed aroundthese. Excellent post-operative revoery with rapid relief of jaundice occurred. The patient has remained in good health, apart from further attacks of pyelonephritis.

CASE 19. A.G., a 59 year old female clerk. History of intermittent jaundice for four months. Partial gastrectomy had been performed for duodenal ulcer four months prior to her present admission and cholecystectomy was done at the same time. This was followed by increasing jaundice with pale stools and dark urine. No previous history of renal disease.

Examination: Afebrile, deeply jaundiced. No stigmata of liver failure. B.P. 135/80 mm. Hg.

Laboratory Investigations: Hb. 10.7 G.%. W.B.C. 4,900 per cu. mm. Serum bilirubin 14.2 mg/100 ml. Serum proteins: albumen 5.1 G.%, globulin 2.2 G.%. Thymol turbidity 1 unit. Zinc sulphate turbidity 1 unit. Serumalkaline phosphatase 82 K-A units.

Urine examination: Normal.

The patient was transfused with the red cells from 3 pints of blood.

Operation was performed one month after admission. This revealed stenosis at the confluence of the hepatic ducts, later shown to be due to an adenocarcinoma of the ducts. A "Y" shaped vitallium tube was inserted into the ducts after resection of the stenosed areas.

The patient made a very satisfactory recovery with gradual disappearance of jaundice over four months, and is still alive and well two years later.

CASE 20. E.L., a 65 year old housewife. Three months history of painless jaundice with pale stools and dark urine. Had been taking chlorpromazine for some months prior to the onset of jaundice. This drug was discontinued at the onset of the jaundice. No previous history of renal disease.

Examination: Deeply jaundiced, afebrile. No stigmata of liver failure. B.P. 140/80 mm. Hg. Liver enlarged 10 cm. below the costal margin. No splenomegaly.

Laboratory Investigations: Hb. 10.4 G.%. W.B.C. 5,900 per cu. mm. Serum bilirubin 10.2 mg./100 ml. Serum proteins: albumen 4.6 G.%, globulin 3.0 G.%. Serum electrophoresis showed an increase in β globulin. Thymol turbidity 1 unit. Zinc sulphate turbidity 6 units. Serum alkaline phosphatase 78 K-A units. S.G.O.T. 52 units. S.G.P.T. 50 units.

Urine: Normal. Culture sterile.

The patient was given a course of steroids, without any effect on the jaundice.

Laparotomy was performed one month after admission. This showed a firm, nodular, bile-stained liver, with no abnormality of the extra-hepatic biliary tree on cholangiography. Liver biopsy showed histological changes of intrahepatic biliary obstruction

The patient made an entirely satisfactory post-operative recovery. The jaundice persisted. Six months later, she developed pneumonia, which was resistant to antibiotic therapy. The pneumonia was complicated by supra-ventricular tachycardia and in addition she developed a urinary infection. Despite vigorous therapy, she developed terminal cardiac and renal failure.

Post-mortem examination showed early biliary cirrhosis. The kidneys were rather small and the site of acute and chronic pyelonephritis.

CASE 21. A.M., a 65 year old housewife. Three months history of upper abdominal pain, loss of appetite and loss of weight. Jaundice with pale stools and dark urine for three weeks. No previous history of renal disease.

Examination: Afebrile, marked jaundice, no stigmata of liver failure. Liver enlarged 10 cm. below the costal margin. B.P. 140/90 mm. Hg.

Laboratory Investigations: Hb. 11.8 G.%. W.B.C. 6,000 per cu. mm. Serum bilirubin 12.1 mg./100 ml. Serum proteins: albumen 4.5 G.%, globulin 1.9 G.%. Thymol turbidity 3 units. Zinc sulphate turbidity 3 units. Serum alkaline phosphatase 48 K-A units.

Urine examination: Normal. Culture sterile.

Operation three weeks after admission revealed a large adenocarcinoma of the head of the pancreas with extensive lymph gland involvement. Cholecystjejunostomy and a gastro-enterostomy were performed.

Post-operative recovery was satisfactory with fading ofthe jaundice. However, the patient developed ascites and glycosuria four weeks after operation. Her general condition rapidly deteriorated and she died at home two months post-operatively. No post-mortem examination was performed.

CASE 22. E.H., a 64 year old housewife. Two week history of upper abdominal pain and jaundice with pale stools and dark urine. No previous history of renal disease.

Examination: Very stout, jaundiced lady. Intermittent fever to 102°F. No stigmata of liver failure. Marked tenderness under the right costal margin, with an ill-defined mass in this region. B.P. 145/95 mm.Hg.

Laboratory Investigations: Hb. 13.5 G.%. W.B.C. 12,000 per cu. mm. with 80% neutrophil polymorphs. Serum bilirubin 9.2 mg./100 ml. Serum proteins: albumen 4.2 G.%, globulin 2.1 G.%. Thymol turbidity 1 unit. Zinc sulphate turbidity 5 units. Serum alkaline phosphatase 66 K-A units.

Urine examination: Normal. Culture sterile.

The patient was initially treated with antibiotics, which controlled the fever.

Operation was performed two weeks after admission and revealed an empyema of the gall bladder with multiple small stones in the biliary passages. Cholecystectomy was performed. Cultures of pus from the gall bladder grew coliform bacilli.

Post-operatively, antibiotic therapy was continued and the patient progressed very satisfactorily. The jaundice rapidly faded.

CASE 23. C.S., a 52 year old housewife. Three months' history of malaise and mild anorexia with two months painless jaundice; pale stools and dark urine. Two stone loss in weight in six months. No previous history of renal disease.

Examination: Deep jaundice; afebrile; mass in the right upper quadrant of the abdomen. B.P. 130/85 mm.Hg. No stigmata of liver failure.

Laboratory Investigations: Hb. 8.6 G.%. W.B.C. 6,900 per cu. mm. Serum bilirubin 18 mg/100 ml. Serum proteins: albumen 4.6 G.%; globulin 1.8 G.%. Thymol turbidity 1 unit. Zinc sulphate turbidity 2 units. Serum alkaline phosphatase 74 K-A units. Urine examination: Normal. Culture sterile.

The patient was transfused with the red cells from 3 pints of blood.

Operation was performed one week after admission. There was an extensive carcinoma involving the gall bladder and biliary system. Removal of the tumour was impossible. A polythene tube was inserted into the upper end of the common bile duct and carried down to the duodenum. A gastro-enterostomy was also performed.

The patient made a good post-operative recovery but there was little change in the jaundice. Serum bilirubin on discharge was 17.7 mg./100 ml. Her general condition deteriorated rapidly following discharge and she died at home six weeks after operation. No post-mortem examination was performed.

CASE 24. E.S., a 39 year old housewife. This lady had had a cholecystectomy carried out at another hospital two weeks before her admission here. She had not been jaundiced before this operation, but a stone was removed from the common bile duct. She developed high fever on the second post-operative day with deepening jaundice associated with dark urine and pale stools. Her fever was controlled with antibiotics, but the jaundice deepened. Previous health good, with no history of renal disease.

Examination: She was deeply jaundiced, afebrile and well-hydrated. There were no stigmata of liver failure. B.P. 140/80 mm.Hg.

Laboratory Investigations: Hb. 10.1 G.%. W.B.C. 4,800 per cu. mm. Serum bilirubin 5.8 mg./100 ml., on admission. Serum proteins: albumen 6.2 G.%, globulin 1.4 G.%. Thymol turbidity 1 unit. Serum alkaline phosphatase 41 K-A units.

Urine: Normal. Culture sterile.

The patient was observed for 2 weeks, during which time she remained afebrile, but her serum bilirubin rose slightly to 6.0 mg./100 ml.

Laparotomy was performed two weeks after admission, and showed obstruction of the upper part of the common bile duct by an inflammatory mass. This obstruction extended for 0.5 - 1 cm.

The common bile duct was reconstructed over a polythene tube, which was brought out through the duodenum to the surface.

Post-operative progress was completely uneventful. Her jaundice rapidly improved. The polythene tube was removed and the patient has remained well and free of jaundice.

CASE 25. J.S., a 50 year old housewife. Two weeks history of intermittent abdominal pain with jaundice. Similar illness three years previously which cleared up spontaneously. No previous history of renal disease.

Examination: Afebrile, deeply jaundiced. No stigmata of liver failure. B.P. 150/85 mm.Hg.

Laboratory Investigations: Hb. 12.4 G/100 ml. W.B.C. 6,000 per cu. mm. Serum bilirubin: 20 mg./100 ml. Serum proteins: albumen 5.8 G/100 ml., globulin 2 G/100 ml. Thymol turbidity less than 1 unit. Zinc sulphate turbidity 3 units. Serum alkaline phosphatase 64 K-A units.

Urine examination: Normal. Culture sterile.

Operation was performed one week after admission and revealed a large stone impacted at the lower end of the common bile duct. This was removed and cholecystectomy performed.

Recovery from the operation was satisfactory apart from transient paralytic ileus. The jaundice gradually faded and the patient was discharged completely well.

<u>CASE 26.</u> <u>G.W., a 69 year old housewife.</u> Chronic bronchitis for many years, with incipient heart failure during the last year, treated with digitalis and diuretics. History of intermittent upper abdominal pain for many years, with occasional transient jaundice. Six weeks prior to admission she developed persistent jaundice with pale stools and dark urine. Four days before admission, her abdominal pain became more severe and was accompanied by retching and vomiting. On the same day, she developed diarrhoea, passing loose, pale stools every two hours. On the following day she passed no urine and, indeed, was almost completely anuric until admission. On the same day in the late evening she passed dark stools (?melaena). She was admitted to another hospital on the following day, and transferred to this hospital on the same day. There was no history of previous renal disease, and her doctor knew her to be normotensive.

<u>Examination:</u> On admission to this hospital she was afebrile, deeply jaundiced, semi-comatose and dehydrated. No heart failure and no stigmata of liver failure. Blood pressure between 90/50 and 125/60 mm.Hg.

<u>Laboratory Investigations:</u> Electrocardiogram: Sinus rhythm with many ventricular ectopic beats.

Hb. 11.5 G/100 ml. W.B.C. 7,000 per cu. mm. Blood urea on admission: 273 mg./100 ml. Serum potassium 8.4 m.eq/litre; sodium 137 m.eq/litre; chloride 95 m.eq/litre; bicarbonate

16 m.eq/litre. Faeces: No blood present.

No urine obtained by catheterisation.

The patient was given rectal cation exchange resins, intravenous glucose, insulin and calcium gluconate. In addition, she was rehydrated with intravenous fluids and given intravenous hydrocortisone. Overnight her general condition improved. Haemodialysis was carried out, which corrected her hypokalaemia and reduced her blood urea to 70 mg/100 ml. She was established on a routine anuria regime and after seven days' complete anuria, began to pass increasing amountsof urine. Haemodialysis was repeated on the twelfth day. Her general condition remained satisfactory and there was no evidence of infection. Her blood pressure remained rather low at 100/60 mm.Hg. She appeared to be recovering satisfactorily, her urinary output having risen to 1800 ml. in 24 hours and her blood urea falling to 80 mg/100 ml; the jaundice was also fading. On the 35th day after admission she developed signs of acute peritonitis.

Operation confirmed perforation of a chronic duodenal ulcer. This was sutured. A limited operation was performed and no obvious cause for her jaundice was demonstrated. The patient did not tolerate the operation well. She developed acute bronchopneumonia and acute right heart failure. Her urinary output again fell, she had persistent hypotension and on the sixth post-operative day her abdominal wound ruptured. This was resutured but the patient's condition rapidly deteriorated and she died within a few days.

Necroscopy showed bilateral bronchopneumonia and a small wound abscess. The presence of a chronic duodenal ulcer was confirmed, the repaired perforation being intact. There were many calculi throughout the biliary tract. The liver was slightly bile-stained but otherwise appeared normal macro-and microscopically. The kidneys were of normal size but showed evidence of mild arteriosclerosis. On histological examination there was evidence of severe tubular degeneration.

CASE 27. F.L., a 69 year old housewife. Two day history of anorexia and upper abdominal pain. Intermittent upper abdominal pain for years and winter bronchitis for many years. She was jaundiced on admission, but had not observed this herself and did not know how long it had been present. No previous history of renal disease.

Examination: Obese, jaundiced lady, with a temperature of 101°F. Not dehydrated and no stigmata of liver failure. No evidence of heart failure. B.P. 90/40 mm.Hg. Tender under the right costal margin.

Laboratory Investigations: Hb. 12.7 G.%. W.B.C. 26,400 with 91% neutrophil polymorphs. Serum bilirubin 4.9 G./100 ml. Blood urea 90 mg./100 ml. Serum amylase less than 3 Wohlgemuth units. Serum sodium 139 m.eq./litre. Serum potassium 3.7 m.eq./litre. Serum chloride 95 m.eq./litre. Serum bicarbonate 21 m.eq./litre.

Electrocardiogram: Normal.

Urine: Protein present. Slight excess of red blood cells. Sterile on culture.

On admission the patient was diagnosed as having acute cholecystitis and was treated with tetracycline. Within 24 hours it was apparent that she was oliguric, the urine contained protein and was of low specific gravity (1009). Urine plasma/

urea ratio was 2:1. Her temperature returned to normal in four days and her white blood count fell to normal. Her blood pressure, however, remained low, despite intravenous fluids and blood transfusion. Treatment with cortisone acetate, 250 mg. twice daily, intramuscularly was commenced on the sixth day after admission. By this time her blood urea had risen to 410 mg./100 ml. and haemodialysis was performed on the following day. Following this, and in association with steroid therapy, her blood pressure rose to 120/60 mm.Hg. and in a few days to 140/90 mm.Hg. Her urinary output improved, and she made a slow but uninterrupted recovery with return of renal function and disappearance of the jaundice. A cholecystogram failed to demonstrate the biliary system and the patient refused to have further investigation of the cause of the jaundice.

CASE 28. J.L., a 40 year old male street trader. This patient was transferred from another hospital with renal failure. He had been admitted to this hospital with a ten day history of jaundice, pale stools and dark urine. There was a six year history of chronic duodenal ulceration. There was no previous history of renal disease or of drug ingestion.

Examination on admission revealed marked jaundice. No stigmata of liver failure. Slight hepatomegaly. B.P. 130/80 mm.Hg. Temperature 99°F. on admission falling to normal over six days.

Laboratory Investigations at this time: Hb. 12.5 G.%. W.B.C. 10,000 per cu. mm. with 73% neutrophil polymorphs. Serum bilirubin 7.3 mg./100 ml. Serum proteins: albumen 4.2 G./ 100 ml., globulin 2 G./100 ml. Serum alkaline phosphatase: 22 K-A units.

Urine: Trace of protein. No other abnormality.

Operation was performed two weeks after admission, when the serum bilirubin had risen to 11.2 mg./100 ml. No extra-hepatic obstruction was demonstrated. The operation was difficult because of severe haemorrhage, but there was no hypotension, either during the operation or during the next few days. The patient recovered from the anaesthetic and prognossed satisfactorily. Urine output was normal. On the fourth post-operative day the patient's temperature rose to 100.4° and there was oozing of blood and bile from the abdominal wound three days later. The wound was explored on the 14th post-operative day. The abdominal cavity was found to be full of blood and bile. The wound was drained and resutured; the fever settled following this. There was no hypotension; the blood pressure being 140/90 - 130/70 throughout the period.

Following the second operation the patient developed progressive oliguria. The biochemical data for the period following his first operation had been lost, but although the jaundice persisted, there was no rise in blood urea until following the second operation, coinciding with the oliguria. He was transferred to this hospital four days after his second operation, when his blood urea was 320 mg./100 ml. and serum potassium 5.8 m.eq./litre. On admission he was confused, acidotic, and deeply jaundiced. B.P. 130/60. Afebrile.

Investigations: Hb. 5.9 G.%. W.B.C. 27,000 per cu. mm. with 80% neutrophil polymorphs.

The urine contained protein and was of a fixed specific gravity (1010).

He was established on an anuria regime and dialysed on the day following admission, using regional heparinisation.

At the same time the patient was given four pints of blood. His general condition markedly improved. This improvement was maintained and the urine output gradually rose over four days to 1250 ml./24 hours. Further blood transfusions were given during this time and the patient appeared to be making satisfactory progress, when he suddenly developed severe gastro-duodenal bleeding, and despite massive blood transfusion, died before surgery was possible.

Post-mortem examination revealed a chronic duodenal ulcer, which was the source of massive haemorrhage. There were two small pockets of pus in relation to the upper end of the bile duct. The liver was enlarged and bile stained, but there was no evidence of extra-hepatic biliary obstruction. Histological examination showed changes compatible with primary intra-hepatic biliary stasis. The kidneys were of normal size but rather pale. Microscopic examination showed the changes typical of bile nephrosis with rather marked tubular degeneration, but no gross tubular necrosis.

CASE 29. E.J., a 61 year old male insurance broker. Six weeks' history of upper abdominal discomfort and four weeks jaundice with pale stools and dark urine. Mild anorexia but no vomiting or diarrhoea. No fever. No previous history of renal disease.

Examination: Jaundiced. No stigmata of liver failure. Afebrile. Liver markedly enlarged and gall bladder easily palpable. B.P. 160/90 mm. Hg.

Laboratory Investigations: Hb. 10.7 G.%. W.B.C. 14,000 per cu. mm. with 84% neutrophil polymorphs. Serum bilirubin 5.5 mg./100 ml. Thymol turbidity 0.9 units. Zinc sulphate turbidity 1.1 units. Serum alkaline phosphatase 28 K-A units.

Urine examination: Normal.

This patient was not seen before operation and blood urea and serum electrolyte estimations were not done.

Operation three days after admission revealed a small, localised carcinoma of the head of the pancreas, without evidence of metastases.

A radical operation was embarked on (Whipple's operation). Part of the stomach, all the duodenum, part of the jejunum, part of the common bile duct and the head of the pancreas were removed. This proved to be a long and difficult procedure, but it was well tolerated by the patient without hypotension. The operation lasted five hours. Three pints of blood were given at the end of the operation.

The patient recovered normally from the anaesthetic and his clinical condition appeared satisfactory for 48 hours, although it was noted that he was oliguric and his urine contained protein. There is no record of the blood pressure after operation for the first 48 hours. When first seen by me on the third post-operative day, the patient was feverish and confused. The blood urea had risen from 68 mg./100 ml. on the first post-operative day to 210 mg./100 ml. The urine contained protein, had a specific gravity of 1009 and urine: plasma urea ratio of 2:1. Serum potassium 5 m.eq./litre. The blood pressure at this timewas 110/60 mm.Hg. and the haemoglobin was 9.8 G./100 ml., W.B.C. 18,400 per cu. mm. with 91% of polymorph leucocytes. Despite massive antibiotic therapy and use of vasopressor agents, his fever was not controlled and his blood pressure remained rather low. The oliguria persisted and the patient was dialysed on two occasions. His condition was only temporarily improved by this and he died on the 16th post-operative day. Treatment with intravenous hydrocortisone, 100 mgm. 6-hourly was only begun two days before death.

Post-mortem examination revealed widespread peritonitis with pockets of pus between the coils of small intestine and a large collection of pus in the lesser sac. It was evident that there had been considerable leakage from the pancreatico-jejunal anastomosis. The liver was bile stained and slightly enlarged, but showed no evidence of cirrhosis. Histologically the kidneys showed the changes typical of extensive tubular necrosis, with some evidence of epithelial regeneration.

CASE 30. W.L., a 64 year old male aircraft inspector. History of intermittent abdominal pain for three months with three weeks of jaundice. Moderate loss in weight. No previous history of renal disease.

Examination: Deep jaundice. No stigmata of liver failure. B.P. 220/110. No abnormal findings in the abdomen.

Laboratory Investigations: Hb. 13.9 G./100 ml. W.B.C. 10,300 per cu. mm. with normal differential count. Serum bilirubin 16.1 mg./100 ml. Serum proteins: albumen 5.2 G.%, globulin 2.4 G.%. Thymol turbidity 1 unit. S.G.O.T. 27 units. S.G.P.T. 30 units. Blood urea 25 mg./100 ml. Serum potassium 4.2 m.eq./litre. Serum sodium 130 m.eq./litre.

Urine examination: Specific gravity 1018. Normal.

The patient was not seen before operation, which was performed six days after admission.

Operation revealed a large carcinoma of the head of the pancreas, obstructing the common bile duct. Choledocho-jejunostomy and jejuno-jejunostomy were performed. No record was available of the blood pressure during operation. The patient was transfused with one pint of blood during surgery.

The patient recovered from the anaesthetic normally, but was oliguric, throughout his post-operative period. The urine contained protein and its specific gravity was 1010. A blood pressure of 130/70 was recorded on the first post-operative day. The patient was afebrile throughout the whole post-operative period. When first seen on the second day after operation, he appeared dehydrated, hypotensive (blood pressure 90/70) and in circulatory failure. His blood urea had risen to 193 mg./100 ml. and serum potassium to 6.5 m.eq./litre. Haemoglobin at this time was 13.3 gm./100 ml.

He was given a test infusion of 1,500 ml. of 1/5 N saline with 4% glucose, which raised the blood pressure to 130/70 but did not produce a diuresis. The serum potassium was controlled by Resonimum-A cation-exchange resin given rectally. He was then established on the routine anuria regime of restricted fluid and protein intake. The blood pressure remained at the 130/70 level. Haemodialysis was carried out on two occasions with temporary improvement. There was no evidence of infection, but on the 14th day post-operatively the abdominal wound burst. This was resutured but the patient died on the following day.

<u>Post-mortem examination</u> revealed an extensive adenocarcinoma of the pancreas, which was involving the lower end of the bile duct. The anastomosis was intact and patent and there was no evidence of biliary leak or of cholangitis. Lymph gland and hepatic metastases were not present. The lungs showed terminal broncho-pneumonia. The kidneys showed well marked arterio-

sclerosis, they were oedematous and pale. On microscopic examination, the renal tubules were dilated and contained numerous casts. The epithelial cells showed patchy degenerative changes with vacuolation and there was moderate infiltration of the interstitial tissue with inflammatory cells.

The appearances were compatible with ischaemic necrosis, superimposed on a moderately nephrosclerotic kidney.

APPENDIX II

Chemical methods for clinical laboratory investigations.

Serum bilirubin - diazotized sulphanilic acid method - (Dangerfield and Finlayson, 1953)

Blood urea - Technicon Autoanalyser; Diacetyl Monoxamine method (Marsh et al, 1957)

Serum alkaline phosphatase - Technicon Autoanalyser; 4 Aminoantipyrine method (Powell and Smith, 1954)

Thymol turbidity - (MacLagan, 1944)

Zinc Sulphate Flocculation - (Kunkel, 1947)

Serum Glutamic Oxalacetic and Glutamic Pyruvic Transaminase - colorimetric method (Reitman and Frankels, 1957)

Serum proteins - Biuret method (Gornall et al, 1949)

Experimental methods

Inulin and Para-amino Hippurate Clearance

Humans

The procedure employed was based on that of Smith (1956).

Clearance studies were performed in the morning, commencing between 8 and 9 a.m. Patients were confined to bed on the morning of the test and were given 1000 ml. of fluid to drink between waking (6 a.m.) and 8 a.m. No drugs, smoking, strong tea or coffee were allowed. A light breakfast - weak tea and buttered toast - was given at 7:30 a.m. Bladder catheterisation was NOT performed except in cases shown to have difficulty in evacuating their bladder. Intravenous infusions were set up without the use of local anaesthetic. At this time, 15 mls. of blood was obtained for urea and creatinine estimations. Urine specimens were obtained before infusion of Inulin or P.A.H.

An adequate rate of urine flow was ensured throughout the test by the intake of 200 ml. of water per hour.

To establish a plasma concentration of Inulin of 25 mg./100 ml. ± 5 mg./100 ml., and of P.A.H. of 2-4 mg./100 ml., a loading solution containing 50 mg. per kg. body weight of Inulin and 5.8 mg./kg. of P.A.H. made up in 200 ml. of normal saline, was infused at a rate of 10 ml. per minute. Inulin for intravenous infusion was obtained as a 10% solution in 25 ml. ampoules (Thomas Kerfoot and Co. Ltd.). This super-saturated solution was carefully and completely redissolved prior to making up test infusions on the day of the investigations. Para-amino-hippurate was obtained as the sodium salt of para-amino-hippuric acid (L. Light and Co. Ltd.) and was made up as a 10% solution in 10 ml. ampoules under sterile conditions in the Hospital Dispensary.

All infusions were made up under strict aseptic conditions. Loading infusions were followed by constant maintenance infusions at a rate of 4 ml. per minute. The solutions were made up to give 0.57 mg/kg/min. of Inulin and 0.23 mg/kg/min. of P.A.H. Normal saline was used as the carrier solution for these infusions. Urine collections were commenced at least

30 minutes after commencing the maintenance infusions.

Because bladder catheterisation was not routinely carried out, collection periods of at least 20 minutes were employed with urine flow rates of 1.5-2 ml. per minute. Longer periods were used with slower rates of urine flow. Heparinised blood samples were obtained from the contra-lateral-arm at the commencement and midpoint of urine collections. Throughout the test a record was kept of pulse rate and blood pressure.

At least three consecutive collection periods were employed.

Analytical Methods

All blood and urine samples were analysed on the day of collection. All analyses were done in duplicate and reagent, blood and urine blanks were included inall instances. These methods of analysis conformed to the recommendations suggested by Smith (1956).

Protein Precipitation

Blood samples were centrifuged at 3,500 r.p.m. and the plasma separated. Plasma protein was precipitated by the method recommended by Smith (1956) modified from Somogyi (1930).

Inulin Estimation

Inulin was measured colorometrically using the direct resorcinol method without alkali treatment (Schreiner, 1950).

Standard solutions containing 1, 2, 3 and 4 mg./100 ml. of Inulin were included in each set of estimations.

Para-amino-hippurate Estimation

The analytical method employed was that of Bratton and Marshall (1939), modified by Smith et al (1945). Duplicate estimations were carried out in all instances and a reagent blank and three P.A.H. standards of 0.1, 0.2 and 0.4 mg./100 ml. included in each instance.

Calculation of Clearances

Clearance values were calculated, using the conventional formula.

$$\text{Clearance} = \frac{U \times V}{P}$$

where U = Urine concentration of Inulin or P.A.H. in mg./100 ml.

V = Rate of urine flow in ml./min.

and P = Plasma concentration in mg./100 ml.

Measured plasma values were plotted against a time scale and the value obtaining 6 minutes before the mid point of each urine collection period was calculated. Clearance values that differed by more than 5% were discarded.

Dogs

The technique employed for performing clearances on dogs was similar to that suggested by Smith (1956). The dogs were studied in the fasting state, although fluid was allowed as desired. No specific fluid loading by gavage was employed. Dogs were anaesthetised with intravenous pentobarbitone sodium (Nembutal: veterinary) in a dose calculated to produce light general anaesthesia. This was usually 60 mg. for 5 lb. body weight, but was less in the case of the jaundiced dogs. All dogs were intubated with endo-tracheal tubes.

Intravenous infusions were made continuously into a foreleg vein and blood pressure recordings and blood samples obtained via a polyethylene cannula inserted into a femoral artery.

All dogs were catheterised with strict asepsis and a urine specimen was cultured on each occasion. Urine and blood blanks were obtained before infusions of Inulin and P.A.H. were set up.

Loading solutions containing Inulin and P.A.H. were made up to contain 92 mg./kg. of Inulin and 38 mg./kg. of P.A.H. The total volume of this infusion was made up to 200 ml. with normal saline. Maintenance infusions were made up to deliver1.4 mg./kg./minute of Inulin and 0.35 mg./kg./min. of P.A.H. and infused at a rate of 2 ml. per minute. Collection periods commenced at least 30 minutes after the setting up of the maintenance infusion. The bladder was emptied at the beginning and the end of collection periods by firm suprapubic compression. Two or three consecutive washouts were then performed with 20 ml. of normal saline followed by equal amounts of air. The collection period was timed from the last installation of air. At least two, and in most cases, three consecutive collection periods were employed, each of 10-15 minutes. Blood samples were obtained at the beginning of each period and at the end of the last collection period. The haematocrit was determined on blood samples taken during clearances and from this the whole body haematocrit was calculated.

The same analytical methods were used to estimate Inulin and P.A.H. as were used in the patients. Clearances were calculated in the same way.

Renal blood flow was calculated from P.A.H. clearance (C P.A.H.) and whole body haematocrit according to the formula -

$$R.B.F. = \frac{CPAH}{1.00 - \text{whole body haematocrit.}}$$

As mentioned in the main paper, no correction has been made for the extraction of P.A.H.

Mean systolic blood pressures were recorded throughout these studies.

Renal Extraction of Para-amino-hippurate.

The percentage extraction of P.A.H. by the kidney, was calculated from the formula:

$$\frac{\text{Renal vein concentration of P.A.H.}}{\text{Systemic arterial concentration of P.A.H.}} \times 100$$

Renal vein blood was obtained by retrograde catheterisation of the left renal vein under direct vision, using a polyethylene catheter passed up the vena cava from the femoral vein. The tip ofthe catheter was sited in the kidney hilum. Venous blood was obtained, using minimum suction. Arterial blood was simultaneously drawn from the femoral artery.

Endogenous Creatinine Clearances

Procedure

In many instances these were performed at the same time as Inulin and P.A.H. clearances. In all instances the same initial preparations were employed. The bladder was completely evacuated at 8 a.m. (the exact time being noted to the nearest minute) and the urine discarded. The bladder was again evacuated at 10 a.m. and 12 noon, exact times being noted. In many instances patients found they had to empty their bladders more frequently and in this event the time was noted and this period taken as a collection period. Initially two mid-point heparinised blood samples were taken, but as the creatinine content rarely varied, one sample only was obtained in later cases, at 10 a.m.

Analytical Methods

Plasma Creatinine was measured by two methods. Initially the method of Edwards and Whyte (1958) was employed. This method, involving the absorption of creatinine onto Lloyd's reagent and its subsequent elution with alkaline picrate solution was found to be very satisfactory, yielding reproducible results with 98 - 102% recovery. It is, however, time-consuming, and in 1961 a change was made to the equally satisfactory method of Teger-Nilsson (1961). No patient had creatinine clearances determined at different times, using different methods of estimating plasma creatinine.

Teger-Nilsson Method

Small ion-exchange columns made up with Dowex 50 W, grain size 200-400 mesh are used.

Reagents - 0.1 M HCl.

51.3 mM Picric Acid Solution

Alkaline Picrate Solution pH 12.4 (0.80 ml. of 0.50 M NaOH added to 10 ml. 51.3 mM picric acid solution)

Phosphate Buffer pH 12.4 (50 ml. 0.50 M Na_2HPO_4 and 63 ml. 0.50 M NaOH, diluted to 200 ml. with distilled water)

Stock creatinine standard 100 mg./100 ml. creatinine hydrochloride (Analar) in 0.1 M HCl.

The picrate solution is freshly made on each occasion.

Procedure

Equal volumes of serum and 0.1 M HCl are mixed in a small flask and left for 2-3 minutes to allow CO_2 to evolve. 2.0-4.0 ml. of this mixture is slowly poured on the ion exchange column, which is prepared to run for approximately one hour with this amount of liquid. The column is then washed with 3 ml. of 0.9% NaCl and 5-6 ml. of distilled water. The creatinine is then eluted with 2.0 ml. phosphate buffer solution and the eluate collected in a test tube containing

1.0 ml. of alkaline picrate solution. This is then allowed to stand for a further 30 minutes when the colour produced is read in a Unicamb S.P. 600 spectrophotometer at 510 mμ. in a 10 mm. curette. All estimations are done in duplicate and a reagent blank and three freshly made standards of 0.5, 1.0 and 1.5 mg./100 ml. creatinine hydrochloride are included.

After use the columns are regenerated by washing with 2 ml. of 2 M NaOH, 2 ml. distilled water, 3 ml. 4 M HCl and distilled water until the effluent is neutral. Columns are stored in distilled water when not in use and renewed after being used four times.

Using this method we have obtained 98-102% recovery of creatinine added to plasma and excellent reproducibility of results. There was no significant difference in the plasma creatinine levels obtained by this method compared with that of Edwards and Whyte.

Urine creatinine was estimated after dilution of the urine 1:100 or 1:200, both using the ion exchange columns and by the classic method of Folin and Wu (1919). Although it has been stated (Edwards and Whyte; 1958) that bilirubinuria may affect the results if creatinine is not first eluted from the urine, we have found little difference in the results obtained by the two methods.

The normal creatinine clearance values using these methods in this laboratory are

males - 116 ml./min. S.E. ± 3.8 (12 males age 20-50)

females - 107 ml./min. S.E. ± 4.2 (10 females age 24-60)

Urine Protein Estimation

All specimens of urine were tested for protein by boiling, and by the addition of 25% sulphosalicylic acid.

Quantitative estimations of protein were performed by a biuret method (Gornall et al 1949) after preliminary concentration with trichloracetic acid.

One dimensional paper electrophoresis was performed by the method of Flynn and de Mayo (1951).

Tests for Glycosuria

Qualitative tests for sugar were made with "Clinitest" tablets, and the presence of glucose confirmed by the use of "Clinistix" glucose oxidase tests.

Urine Amino-acids

The urine amino-acid pattern was determined by paper chromatography by Dent's method (1948).

Urine Concentrating Ability

All patients were given 5 units of an active preparation of vasopressin tannate in oil by subcutaneous injection at 6.0 p.m. In every instance, care was taken to re-suspend the active ingredient in the vials. No fluid was allowed overnight and urine specimens were obtained at 6.0 a.m., 10.0 a.m. and 2.0 p.m. Urine osmolality was determined by freezing point depression.

Test of Urine Acidification

The short test devised by Wrong and Davies (1959) was employed. This test was carried out exactly as described by these authors except that the timing of urine collections was slightly altered. Patients emptied their bladders at 7 a.m. and again at 8 and 9 a.m. They were, at this point, given Ammonium Chloride orally (0.1 Gm. per kg. body weight) and emptied their bladders again at 10, 11 a.m., 12, 2 and 4 p.m. The actual time of emptying was noted to the nearest minute. All urine specimens were immediately taken to the laboratory and either examined at once or stored in the refrigerator in bottles filled to the brim and sealed with screw-top lids. All bottles contained thymol. The urine pH was either determined immediately or at the latest within two hours. Most specimens were fully analysed on the same day. On several occasions specimens were examined on the day of collection and also on consecutive days and in no instance showed significant change in results.

All specimens were analysed for pH, titrateable acidity and ammonium. Initially bicarbonate was also estimated but as negligible amounts were found in urines of pH below 6.00, this was later given up.

Urine pH was determined using a Cambridge glass electrode pH-meter Titratable acidity by back titration to pH 7.4 with 1:20 N NaOH using the pH meter. Urinary ammonium by the micro-diffusion method of Conway (1947). Urine bicarbonate - total CO_2 content by the method of Van Slyke and Neill (1924) and calculation of bicarbonate by the Henderson-Hasselbach equation.

The ammonium chloride used in this test was dispensed in gelatin capsules each containing 0.5 gm. Ammonium Chloride.

Calculations

Bladder emptying was timed to the nearest minute and rates of urine flow calculated for each specimen. From this it was possible to calculate the rate of ammonium and titratable acid excretion. The rate of hydrogen ion excretion was calculated from the formula:

Hydrogen Ion Excretion = Ammonium excretion + titrateable acid excretion - bicarbonate excretion

Renal Conservation of Sodium

All patients studied were established on a standard ward diet, without the addition of table salt. All were given 9 -α- fluorohydrocortisone 2 mg. twice daily. All urine was collected from 6.0 a.m. to 6.0 a.m. on each of three consecutive days. Completeness of collection was checked by estimation of daily creatinine excretion. Urine sodium was measured by flame photometry.

Blood Volume Measurements

Patients

Blood volume measurements were performed using 51Cr. labelled red blood cells to determine red cell volume and the total blood volume calculated from the venous haematocrit estimated at the same time. The method for estimation of red cell volume was that recommended by Mollison (1961). Blood samples were obtained without venous occlusion at 15, 25 and 60 minutes after injection of labelled red cells. The venous haematocrit was determined on each specimen and corrected for trapped plasma (Chaplin and Mollison, 1952). Body haematocrit was calculated by using the value 0.91 to represent the body haematocrit: Venous haematocrit ratio (Mollison, 1961). Blood volume was then calculated from the formula:

$$\text{Blood volume} = \text{Red cell volume} \times \frac{100}{\text{Body haematocrit}}$$

Normal blood volume was calculated from the formula:

Blood volume = Surface area (Sq. M.) X 2.68 litres (Blakeley et al 1962)

Dogs

Because the facilities for measuring blood volume using $^{51}Cr.$ were not readily available, it was decided to use plasma volume estimations using Evans Blue (T.1824.) In dogs simultaneous measurement of plasma volume with ^{131}I albumen and T.1824 gives results which agree within

0.5% (Sear et al, 1953). Plasma levels of T.1824 were measured after extraction from the plasma by the method of Campbell et al (1958). Injections of Evans Blue were made into a foreleg vein using a metal cannula and two-way tap. Injection of the dye was immediately followed by injection of 10 mls. of normal saline. The quantity of Evans Blue delivered was calculated for each syringe by injecting dye from the same syringe into a volumetric flask through the same tap and cannula, followed by 10 ml. of normal saline. This was made up to a known volume and the concentration determined.

Blood samples for dye estimation were obtained before and 15 and 25 minutes after injection. Venous haematocrits were estimated on the same samples and body haematocrits calculated as for patients.

BLOOD PRESSURE MEASUREMENTS IN DOGS

The mean systemic blood pressure was measured during all the experiments carried out on dogs. The femoral artery was exposed in the upper thigh and a polyethelyene cannula inserted and advanced until its tip was estimated to lie in the lower aorta. This cannula was connected through a three-way tap to a conventional mercury "U-tube" manometer. The connection tubing was primed with sterile heparinised saline. The manometer was standardised to read 0 mm./Hg. at the level of the operating table. A very damped pulse wave was obtained in the manometer and systemic pressure was recorded from the top of the mercury column visually. Considerable care was taken throughout all experiments to reduce to a minimum, flushing of the arterial cannula, and so prevent additional fluid loading of the animals.